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PRESIDENTIAL ADDRESS

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NEW YORK, N. Y.

IT IS my privilege to open this general session of the Eighth Annual Meeting of the American Academy of Pediatrics. Those who are here represent 1,229 recognized pediatrists from forty-seven states of the Union, the District of Columbia, Hawaii, and five Provinces of Canada. To have been elected president of such an organization is an honor of honors, and I thank you most humbly for having placed on my unworthy shoulders the mantle worn by my distinguished predecessors.

Since our last meeting, two of our most valued fellows have passed from our circle. It is just and fitting that a word of appreciation should be recorded here.

In the death of Dr. Barnet E. Bonar, the Academy has lost one of its early and most assiduous workers.

Dr. Bonar was a member of the first regional committee of Region IV. He took a great deal of interest in the Academy and was especially active in the work in Utah and Idaho.

Dr. Bonar did not confine his work to pediatrics but did a large amount of obstetrics and as a consequence would not, under present conditions, be eligible for membership in the Academy, but his chief interest was always pediatrics and his investigative work was confined to pediatric subjects, especially concerning the newborn infant.

In a region where very little investigative work has ever been done, Dr. Bonar, by his industry and persistence, succeeded in turning out several very good pieces of work. He became nationally known as a result of this work and several years before he died was elected to membership in the American Pediatric Society. His was a genial, placid character, of rare good humor and the friendliest of spirits. He was an excellent clinician, and his patients loved him. His colleagues trusted him as is indicated by his various positions in the local com-

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munity where he was on the Utah State Board of Health and had been secretary of the Salt Lake County Medical Society.

The Academy and the members of the Academy have lost a friend in the tragic death of Dr. Bonar, and we cannot but feel his loss when we gather together, especially in this western country.

Dr. Louis Schroeder's life was one of ceaseless, unfaltering effort to make the most of his opportunities and to do his bit. With no backing but his own indomitable courage, he passed from high school to a job in a carriage factory. By hard work he saved enough money and studied enough at night to obtain admission to the College of Physicians and Surgeons in New York, from which he graduated in 1911. His ability won immediate recognition, and after serving in medicine as intern at Bellevue Hospital and in pediatrics as intern and resident, he was picked by such men as John Howland and Oscar Schloss for important administrative and teaching positions. He was intensely practical, and it was that characteristic which attracted students and patients. Always abreast of the times, he applied knowledge where it would do the most good.

Louis Schroeder gave freely of all he had, too freely for his own health. Utterly fearless, he fought every wrong or reactionary force he met. He gave his best to this Academy as a regional chairman, to his hospital, to the American Child Health Association, to the Boy Scouts, in the reorganization of whose health work he was actively engaged up to the time of his death, and to many other activities. He loved children, understood them, and served them well.

Besides all of this work he was an omnivorous reader on many subjects, an ardent student of Shakespeare, an eager and appreciative listener to music, and a sculptor of merit. He was a founder and an active booster of the Physicians' Art Exhibition held every year at the New York Academy of Medicine.

Never afraid, he always took a strong stand for what he thought right, but withal he was tolerant and fair. With a fine sense of humor, a knack for telling stories, and a cheerful disposition, he will be missed by a host of friends. It may be truly said of him that the world was a little better for his having lived.

This general meeting is held to hear the reports of the regional chairmen and those of special committees, to evaluate the work done, and, looking ahead, to consider what we shall do next to carry out our specific purposes: (a) to establish and maintain the highest possible standards for pediatric education in medical schools and hospitals, pediatric practice, and research; (b) to perpetuate the history and best traditions of pediatric practice and ethics; (c) to maintain the dignity and efficiency of pediatric practice in its relationship to public welfare; (d) to promote

publications and encourage contributions to medical and scientific literature pertaining to pediatrics.

These reports have all been distributed to you, and I hope you will read them through from start to finish; they are well worth it. And what is more to the point, these reports are presented to *you*, not to the Executive Board. This is your Academy, not the Executive Board's. The fellowship as a whole is strangely and often discouragingly silent concerning what has been done and what might well be undertaken. The Executive Board exists to carry out your wishes as far as it is practicable to do so. It would like more suggestions from you. Dr. Morse warned you in his presidential address that what you get out of the Academy will be according to what you put in.

This is the first and last time that I shall address you as president and, before I return to a peaceful fellowship in the Academy, I want to call your attention to certain parts of some of those reports, and to make a suggestion or two.

Committee on Immunization Procedures.—I feel that Dr. Toomey's committee has done a great service to the fellows of the Academy and to the profession at large by its frank, brief report. None of us are more familiar with the evidence concerning the results of immunization than the members of that committee. They have presented a statement of our actual proved knowledge on these various procedures and, while some of us may be more optimistic concerning certain methods than they are, they have helped us to make our own decisions or to keep our minds open.

Many of us are pestered by conscientious but overenthusiastic parents to carry out all kinds of preventive procedures, some of which we do not approve. One friend of mine tells me he carries this report about with him in his bag to show to parents when overpressed.

I hope the committee will be continued and will be asked, as occasion demands, to submit any changes which should be made. The Academy should make this a "loose-leaf" or "living" document for the guidance and help of its fellows.

It has been suggested, and may be well, that we should prepare and distribute similar reports on methods concerning which such all-embracing claims are made, about certain vitamins, for instance. This is an activity which should be developed.

Committee on Contact Infections.—This committee was appointed by the Executive Board at its December meeting, on the initiative of Dr. Fairfax Hall. He called the attention of the Board to the need for our action. It is a complicated problem, but that it can be met is shown by the success in Westchester County, N. Y.; Knoxville, Tenn.; Newark, N. J.; and other places.

We are all of us only too familiar with the tragic results of exposure of children to infection from their nurses, relatives, and household servants. Dr. Hall has traveled across the continent to present this report, and it is worthy of your careful consideration, discussion, and action. I can think of no more valuable contribution to preventive medicine which this Academy could make than to initiate a campaign such as he outlines. We should not need more evidence than the Knoxville experience, of which he will tell you.

School Health and School Health Education.—Last year Dr. Mitchell's committee presented a report of deep interest which caused much comment. The report this year is of equal importance. The problem of the health of the school child is a very difficult and complicated one. It is one that vitally interests us as an Academy and individually. Over forty-five years ago we began to realize it was a problem. In 1892, New York City appointed one public medical school officer. I am afraid there was more gesture or politics in that than real effort. Two years later Boston appointed fifty physicians, one for each school district, to inspect children for the detection of contagious disease. Chicago became enthusiastic in 1895 and divided the city into nine districts, appointing one inspector for each district, for the same purpose. As each district covered approximately twenty square miles, the effectiveness of the plan may be imagined. In 1897, five years after the appearance of its lone medical school officer, New York City appointed 134 medical inspectors to visit each school daily, again to exclude infectious diseases. Vermont was the first state to officially go further when, in 1903, it passed a law requiring an annual examination of the eyes, ears, and throats of all school children. And so it has gone on—ever increasing in personnel involved and in the millions spent each year throughout the country in discovering physical defects. That is fairly easy; but there the progress has broken down, for the correction of those defects, which should be the object, is a difficult problem. It requires the cooperation of school principal, schoolteacher, school physician, school nurse, *and* parent, *and* private physician. It involves a clash of authority—a division of responsibility.

Ten years or more ago the American Child Health Association carried on a series of investigations on the health of school children, and as a result a continuation study was made by it with funds provided by the Metropolitan Life Insurance Company. The report, entitled "Physical Defects, the Pathway to Correction," was published in 1934 and aroused much interest. Professor Rogers, Dean of Student Health and Physical Education of Boston University, said: "The very least consequence of its publication should be a complete overhauling of medical examination and follow-up services in practically every school in the land."

But the trouble is, how are you going to improve it? It is an intensely practical problem and one that can be solved in its details only by careful trial and retrial. Fortunately, it is being tried out by practical and analytical experts in a limited district in New York City from funds provided from three sources. The interest, cooperation, yes, enthusiasm of the various groups concerned has been secured; each individual step in procedure is studied, new methods tried out in the experimental schools, improved, and then, owing to the interest and splendid cooperation of the Departments of Health and Education, which share the responsibility in New York City, is or will be gradually extended to the whole school system. I mention these New York activities chiefly because Dr. Mitchell participated in all the original studies mentioned and now is district health officer where this tryout is being carried on. He can speak with authority in the report he has presented. The most interesting address I could have made to you, were it permissible, would have been to read you the "Progress Report" of this demonstration, presented to the directing committee by Dr. Dorothy Nyswander, the executive director, two weeks ago.

Until we have a system which has been tried out and proved practicable, we shall blunder on, in the hit or miss method, doing as much effective work as possible. The formation of the American School Health Association is a recognition of the complexity of the problem and the necessity for team work. Succeeding reports from Dr. Mitchell's committee will be awaited with much interest.

Committee on Mental Hygiene.—This whole subject has been one which has baffled us for years. In the White House Conference on Child Health and Protection there was a committee on psychology and psychiatry, of which Dr. Bronson Crothers was chairman. He worked very hard to produce a report which would be constructive, but as far as he and his committee could get was to present "The Problem."

Dr. Beverly's committee has presented a program, and it is to be hoped that a formal course in mental growth and development may be given in our medical schools, but it must be a course given in medical words of one syllable. Dr. Beverly will present this report. It is a very valuable one because it has a definite program to offer, and I believe the Academy should get behind it and push it hard. It is at least an attempt to improve an intolerable situation.

Medical Education.—One of the outstanding contributions of the Academy has been its work for the improvement of the character and scope of pediatric education. Dr. Veeder was chairman of the committee on that subject of the White House Conference, which made a most valuable report, and he, as chairman, and the members of our committee on medical education have rendered invaluable service. In medi-

cine, as in everything else, with a change in ideas the pendulum tends to swing from one extreme to the other and only comes back to a reasonable position after a time.

Thirty-five years ago medical education consisted largely of didactic lectures, recitations, or quizzes, clinics on ambulatory patients, and a smattering of bedside instruction. We "walked the wards," as it was called long ago, a few times; we saw a few operations in a crowded amphitheatre if we could see. That was practically our medical education, apart from simple laboratory work of various kinds, and anatomy. Clinical clerkships were practically nonexistent. Bedside experience we obtained as interns. We went out with our heads very full of book knowledge and learned to apply it in the hospital. Today clinical clerkships are practically universal. That is as it should be. Laboratory work and research have been taking more and more of the time of the undergraduate student. So-called "book learning" has become less and less emphasized. The pendulum has swung a long way. Has it swung too far? I think it has. From my experience of a good many years in examining candidates for internship in a general hospital, I have been increasingly impressed and depressed by the often pathetic lack of knowledge of the principles of medicine and the symptomatology of disease.

Only this past spring a young man came up for examination for internship, concerning whom letters had been received which were very laudatory, and several were personal letters ending, "I really mean this." That man was asked, in oral examination, to give the symptoms of typhus fever. He paused a moment and very calmly replied, "I'm sorry, I am afraid I can't. I never saw a case of typhus fever." And another, equally well recommended, gave as three of the most suggestive early symptoms of scarlet fever, "malaise, anorexia, and a rash."

And in our examinations for the American Board of Pediatrics I have been impressed by the woeful ignorance shown of the "art" of medicine. And I think many other examiners have also.

Several of my precedessors have called attention to this. Dr. Morse said: "The only danger I see is that in some of our Class A schools, in which many or most of the instructors have had no experience in practice, the student may be taught too much laboratory and too little bedside pediatrics. . . . Young men and women, entirely unsuited for research work, are urged to undertake *Arbeits* when they ought to be learning how to keep children well, how to find out what is the matter with them when they are sick, what to do about it, and finally, how to practice medicine. Some men have the scientific mind and are natural investigators. They cannot be kept away from investigation any more than a duck from water. They should be encouraged in every way. Puddles, ponds, and lakes should be provided for them according to

their size and ability. Chickens and young turkeys do not like the water and are not intended to go in the water. Water is bad for them. They should therefore be kept on dry land and not forced into it."

Dr. John Ruhräh said, "In our devotion to the science of pediatrics we are liable to forget that it is also an art. The earlier pediatrists were all art and no science, and our present day graduates are likely to be all science and no art." He also said, "There should be two professors of pediatrics in every medical school, one to teach the science, and one to teach the art."

And let me finally quote a professor of applied physiology in one of our full-time universities. At a stated meeting of the New York Academy of Medicine last February he said: "One may occasionally wish that the premedical education of today might have more science, and the medical education less science and more art."

In the 1937 educational number of the *Journal of the American Medical Association* there are listed fifteen medical schools that require an internship before the degree is granted. During the years 1936 to 1937, 5,484 of the 5,836 graduates of the previous year were interning (nearly 95 per cent).

My experience may be different from that of others. I may be old-fashioned, but I feel that a very valuable contribution of the section on undergraduate education of our committee on medical education would be to investigate how much attention is paid to—for want of a better term—"book-learning." I believe that the medical graduate of my day knew more of the symptomatology of disease when he graduated than the present generation, and I think in that respect he was better equipped.

The American Board of Pediatrics.—The report of the three Academy members of the American Board of Pediatrics is a brief and formal one. It gives you a few facts but tells you little of its activity. I have been a member of that Board since its organization and, while I am accredited as a member of the American Pediatric Society, I would remind you that all nine members are fellows of the Academy.

In his address as our first president, Dr. Abt stated, "In the future deliberations of our organization it will become necessary to define the qualifications of a pediatric specialist."

The Academy accepted this responsibility and was the prime mover in the organization of the American Board of Pediatrics. That Board has done a prodigious amount of work, much of it extremely disagreeable. It has investigated carefully every person applying for certification. It has planned its examinations with care and given them in utter fairness. No candidate is examined by an examiner from his own immediate locality or by one whom he personally knows. The certifica-

tion of 1,226 pediatrists has involved more hard work than you can fully appreciate, and the bulk of that work has fallen upon the Secretary, Dr. Aldrich.

I have mentioned the work of only a few of the committees. All have had important questions to deal with and all have done yeoman service.

What has the Academy done for us individually? Eight years ago there was no country-wide organization open to all qualified pediatrists and to them only. There was the pediatric section of the American Medical Association which was bringing scientific pediatric knowledge to the rank and file of the profession. Good work it has done and long may it continue to do so. There was the American Pediatric Society, a small group, which from the very nature of its organization could not possibly take in all qualified pediatrists, and then there were local groups, large and small, also doing excellent work, many of them, in developing better pediatrics in their own areas.

There were no standards for judging who should be considered as qualified to practice pediatrics as a specialty. I have mentioned our part in the founding of the American Board of Pediatrics. I believe its establishment of standards has been of real value to each one of us, and that it will become of greater importance in the years to come.

The annual meeting of the Academy has provided an opportunity for pediatrists from all over the country to meet together as pediatrists to discuss problems in an informal way at round tables and to present present knowledge, or our lack of it, on important subjects by panel discussions. Its regional meetings have taken up problems of special local interest or importance. All the facts brought out have been made available to the fellows, and to many others, through our Journal.

Besides giving all this information in permanent form, the Journal has provided a much needed addition to American pediatric literature. It does not conflict with other journals because not only is it primarily devoted to practical pediatrics, but the *American Journal of the Diseases of Children* cannot possibly publish all worth-while contributions.

The Academy has made a start in other services to our Fellowship. It has presented an authoritative statement on immunization procedures and will probably render other services along such lines.

It has attempted to help in the development of pediatric research, a field which has been exploited in the name of science to a serious degree, and has resulted in a great waste of money which could have been better used. The Council on Pediatric Research has had a difficult job but it has worked carefully, and we feel it is at a point where definite results may be expected.

In these and in other ways, trivial perhaps individually, but bulking large the Academy has given pediatrics a dignity and a unity which it never had before.

I have taken up enough of your time, perhaps too much. There are many other things I would like to have touched upon. You will hear the report of the executive board from Dr. Helmholz. May I be permitted to say that I entered that board two years ago a novice. It has been a liberal education. Many of its members have served you long, all have served you faithfully, and I have been deeply impressed by their loyalty, their devotion, and their hard work. One has to work on that board, for it has a stern taskmaster in Dr. Grulee; but its members don't mind his driving, for each and every one of us knows that he drives himself ten times harder than he drives us. He has mercy on us, occasionally, but he never has any mercy on himself.

And finally, may I repeat to you, Fellows of the Academy, this is your Academy. Your board and officers have tried to carry out what they think are your wishes. It is greatly to be hoped that your interest and participation will continue and that you will increasingly express your ideas and offer your suggestions. The older Fellows are getting older, so are the younger. We are well launched. It is time the younger men take more initiative.

THE EARLY LESIONS OF POLIOMYELITIS AFTER INTRANASAL INOCULATION

With Comments on Their Relationship to the Early Clinical Manifestations and to the Nonparalytic Cases

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At THE onset of human poliomyelitis certain signs and symptoms appear, almost, if not quite invariably, which are not referable to the spinal cord. Among these may be mentioned fever, vomiting, headache, drowsiness, irritability, affective disturbances, general hyperesthesia, and malaise. It is noteworthy that one or more of these manifestations occur in all recognizable cases of the disease irrespective of whether paralysis eventually develops or not. At this stage abnormalities of the spinal fluid are usually, though not always, present. The appearance of signs and symptoms of involvement of the spinal cord, when they occur, is separated from the manifestations of the onset by a definite interval which may be short or extend over a period of several days.

The origin of the early manifestations has been the subject of much debate. Until recently the theory has been widely popular that they are due to "systemic" or "general" infection without involvement of the central nervous system; that following the "systemic" infection the virus penetrates the choroid plexus and meninges and thus infects the central nervous system.[1] Serious and probably conclusive objections to the "systemic" theory, which have been reviewed elsewhere[2] and which are based on anatomic, pathologic, experimental, and clinical considerations, have led to its virtual abandonment by critical students of poliomyelitis. There remains, however, some disagreement as to the actual channels followed by the infecting virus in entering the body and reaching the spinal cord. It seems fair to state that at the present time the nasal-olfactory-nerve portal of entry is in better harmony with the available evidence and is open to fewer critical objections than others. There is general agreement that the virus is highly, if not exclusively, neurotropic and that preceding trauma (insect bites, lacerations, abrasions, etc.) is not a factor of etiological importance. If these considerations are correct, it is necessary to postulate an all-nerve route from the body surfaces into the central nervous system, and only one such route exists: the olfactory nerve ends in the nasal mucosa, which are actually exposed on the

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surface and connect directly with the central nervous system. It is extremely important in applying the results of experimental work in poliomyelitis to the interpretation of the human disease to remember that no experimental method of inoculation that is dependent on trauma for success is reasonably comparable with the human infection. Certain rare exceptions, such as poliomyelitis following tonsillectomy[3] or prophylactic injections of imperfectly sterilized virus, definitely prove the rule. By such a criterion, the nasal route is the only one supported by adequate experimental evidence; and the others fail conspicuously. Animals can be infected regularly by nontraumatic methods by the nasal route[4] but not by other routes.

The probability that poliomyelitic virus enters the body by the olfactory route raises various interesting and practical questions: particularly, the neural routes by which virus eventually reaches the spinal cord, the lesions or reactions which may be set up along those pathways, and their relationship to the clinical manifestations of the onset and other early nonparalytic stages of poliomyelitis. A continuous route of invasion along nervous pathways alone, extending from the olfactory bulb through the brain stem and thence to the spinal cord, was demonstrated in a previous experimental study,[5] which also showed that a period of about three days elapsed between the appearance of virus in the olfactory bulb and its appearance in the spinal cord. During this interval, virus in large amounts was found in the brain stem. It was therefore suggested that the chief source of the early manifestations of poliomyelitis was the brain stem, particularly the diencephalon (thalamus, etc.).

Attention has been generally focused on the pathologic lesions of the spinal cord, and these have been held to be alone characteristic of poliomyelitis (the term itself denotes an inflammatory disease limited to the cord), so that the occurrence and importance of cerebral lesions are customarily forgotten or overlooked. The observations of Harbitz and Scheel[6] which, with those of E. Müller,[7] remain the most thorough histologic studies of the entire central nervous system in poliomyelitis available in medical literature, bear witness to the fact that inflammatory changes in human patients dying during the acute stage of the disease are constantly present in the central nervous system *above* the cord level, with marked intensity throughout the brain stem, which is involved to a relatively greater degree than the forebrain. These changes, to be sure, are largely perivascular and meningeal (small cell infiltrations and hyperemia) except in the medulla where gross nerve cell changes are not infrequent. Hurst[8] has shown, however, that such changes are in all probability secondary to primary neural invasion by the virus, as are the alterations in the cerebrospinal fluid.

Therefore, while it is probable that during the earliest period of clinical manifestations pathologic lesions are present in the brain

stem, and during this period the disease is really an encephalitis which becomes during the ensuing stages an encephalomyelitis, actual proof that this is true cannot be obtained from human material because patients do not die during the initial stage. We have therefore attempted to obtain information on the point from animal experiment.

Since it is highly probable that under natural conditions poliomyelitis infection enters the body through the olfactory mucosa, the experiments have been designed on that basis.

PROCEDURE

Macacus rhesus monkeys were inoculated intranasally with MV virus by the method of Schultz and Gebhardt[4] and killed at various intervals after inoculation and after receiving injections of trypan blue according to the method, slightly modified, of McClellan and Goodpasture.[9] The average interval after intranasal inoculation and before paralysis in the monkey is a little more than eight days but there is considerable individual variation. Paralysis, while rare before the seventh day and usually present by the tenth, occasionally occurs as early as the fourth and as late as the twentieth day. Infection fails sometimes, but in less than 5 per cent of cases by the method used. Trypan blue stains most of the extranervous tissues but not the intrinsic nervous tissues in the normal animal. According to McClellan and Goodpasture,[9] who worked with herpetic encephalitis in rabbits, damaged nerve cells are stained by the dye given intravitally and hence areas of nerve cell damage become grossly visible. Our own observations which will be presented in detail in the protocols show that areas of capillary hyperemia, even without demonstrable damage to the nerve cells, also become grossly visible mainly from blue stain in the plasma of the distended loops. The time of appearance and distribution of macroscopically visible areas of blue staining in relation to the interval after inoculation, together with histologic changes in various parts of the central nervous system, have been investigated in the present study as a means of observing the evolution of the inflammatory process in the central nervous system during the preparalytic period of poliomyelitis.

One day before the time selected for killing the animal, 25 c.c. of a 1 per cent solution of trypan blue made up in sterile distilled water was given intramuscularly. This was usually done in the afternoon, and the next morning the skin and mucous membranes were found to be stained deep blue.

About two hours before killing, the monkey was given 25 c.c. of the same dye solution intravenously, or sometimes intraperitoneally, as in monkey 9. Some of the samples of dye proved to be toxic, and a number of specimens became useless, for in such cases, presumably because of toxic injury to nerve cells, all the gray matter in the cen-

tral nervous system became intensely and uniformly stained blue. That this had nothing to do with the poliomyelitic infection itself was shown by the occurrence of the same phenomenon in an uninoculated animal intended for a control.

When toxic phenomena did not occur or were slight, the animal was killed under ether anesthesia about two hours later. The jugular veins were cut, and as much blood as would flow with the animal suspended head down was permitted to run out. The carotid arteries were then injected with as much 10 per cent neutral formalin solution as would run in easily by gravity, usually 50 to 75 c.c. This procedure gave an immediate fixation of the central nervous system and prevented post-mortem diffusion of the dye. The brain was then cut sagittally with a long knife into slices of about 2 mm. thickness. Portions of the cord from the cervical, thoracic, and lumbar regions were cut transversely, and other portions from the same regions, longitudinally, into sections of about the same thickness. The cut sections were then run through graded alcohols into absolute alcohol, then into benzene, and finally into a mixture of benzyl benzoate and artificial oil of wintergreen, in which they became transparent and were mounted; the procedure followed, with slight modifications, the Spalteholz technique.

In the control animal, uninoculated with virus, the central nervous tissues proper are unstained or merely show a trace of greenish color in the gray matter. In the inoculated animals a positive reaction is shown by the appearance of areas of definite blue color in the nerve substance, largely confined to the gray matter. For the sake of brevity in description, the intensity of blue staining (as viewed by the unaided eye by transmitted light) has been designated as follows: Grade 1, faint blue; Grade 2, moderate blue; Grade 3, marked blue; Grade 4, very intense blue.

Nearly all the extranervous tissues are stained by trypan blue. Thus, the dura mater was very deep blue; the leptomeninges, a faint blue; the choroid plexus and velum interpositum, a deep blue; the walls of the larger vessels, moderate blue; and the infundibulum of the hypophysis, a moderate blue. These changes occurred, of course, in the control as well as in the test animals.

Microscopic examination was made of several specimens from the control animal (No. 5), No. 6 (three days), No. 24 (four days), No. 9 (five days), and No. 3 (six days); and of a few from No. 4 (seven days), No. 13 (seven days), and No. 2 (nine days). Specimens were taken and examined from various parts of the brain and spinal cord. Stains used were hematoxylin and eosin, cresyl violet, Giemsa, and methylene blue and phloxin. A careful search was made for intranuclear inclusions, which were found only in No. 3 (6 days), and then mainly in the medulla.

The present report is based on the results obtained in eight animals, of which one, the control, was not inoculated with virus; one killed three days; one, four days; one, five days; one, six days; two, seven days; and one, nine days after inoculation. It is a matter of regret that, owing to various technical difficulties, the work could not be extended to afford duplicate studies of any except the seventh day, permitting a fuller sampling of variability, and that some of the specimens intended for microscopic examination were lost.

PROTOCOLS

CONTROL.—Monkey 5, not inoculated with virus, was given 25 c.c. of 1 per cent trypan blue solution intramuscularly on Nov. 24, 1935. On November 25, 25 c.c. of 1 per cent trypan blue solution were given intravenously at 5:30 P.M. The animal was killed two hours later under ether anesthesia by exsanguination, followed by injection of 75 c.c. of 10 per cent neutral formalin solution into the internal carotid arteries.

Gross inspection showed there is no bluish staining of the nervous tissue in brain or spinal cord. The dura mater is intensely blue and so are the choroid plexuses and velum interpositum. The infundibulum of the pituitary is likewise stained deep blue. Similar changes are seen in all the inoculated animals.

Microscopic Examination, Olfactory Bulb.—For purposes of comparison, the microscopic appearance of the normal animal after trypan blue injection is of interest. The pial meshes show no leucocytes or lymphocytes. In the substance, microglial cells are of rare occurrence. Most conspicuous is the large number of small glial nuclei, most of which appear to be oligodendroglia rather than astrocytes, in the mitral and other nerve cell layers. With heavy staining with hematoxylin and eosin, the characteristic chromatin dotting of these nuclei is obscured, and the cells may easily be mistaken for lymphocytes. In thick sections they may cover the nerve cells so that the latter are difficult to find. Visible capillaries are rather widely spaced.

Tissues from other portions of the central nervous system appear quite normal.

THREE DAYS' INCUBATION.—Monkey 6 was inoculated intranasally Jan. 17, 1936, and received intramuscular dye on January 19. Intravenous dye was given January 20, and the animal was killed about two hours later. No temperatures were taken. No paralysis was apparent.

Macroscopic Appearance.—One small spot (1 by 2 mm.) of Grade 2 staining is seen at about the position of the subthalamic nucleus, and faint to doubtful staining just above the roof of the descending cornu of the lateral ventricle. No other areas in brain and spinal cord show any trace of the dye.

Microscopic Examination.—The spinal cord only was examined and found to be normal.

Summary.—Early or doubtful localized reaction in inferior portion of interbrain, and amygdaloid nucleus.

FOUR DAYS' INCUBATION.—Monkey 24 was inoculated Sept. 23, 1936. On September 25 behavior was normal, and temperature 103.6° F. On September 26, behavior was normal, temperature, 104.1° F. Cisternal puncture revealed clear fluid, 108 cells per cubic millimeter. Trypan blue solution was given intramuscularly.

On September 27, behavior was normal; temperature, 104.7° F. At 2:30 P.M. trypan blue solution was given intravenously. At 4:00 P.M. under ether anesthesia,

the carotid arteries were cut, exsanguination performed, and 10 per cent neutral formalin solution injected in the carotid.

Macroscopic Appearance.—The staining as a whole is heavy, and the gray matter throughout the central nervous system shows a faint greenish cast.

Olfactory bulbs are stained blue with more intense staining in a small spot in the anterior pole and more diffusely (Grade 2-3) in the posterior third up to the stalk.

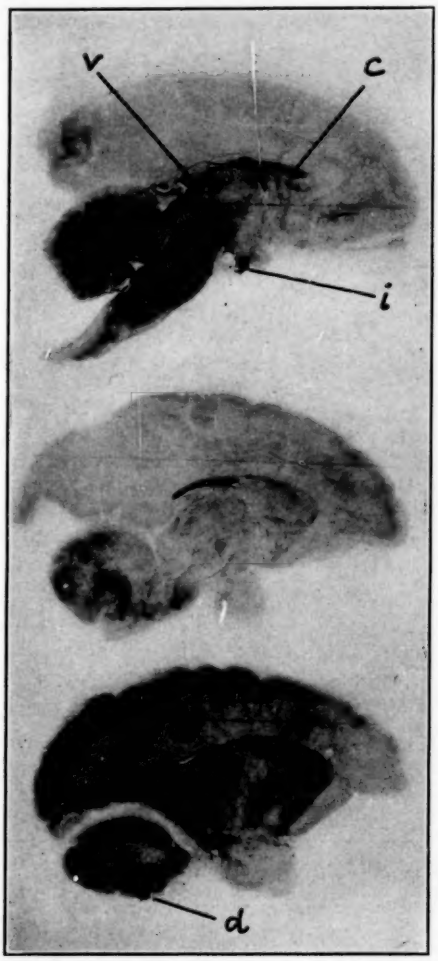

Fig. 1.—Uninoculated control, monkey 5. Blue staining is confined to the choroid plexus (*c*), velum interpositum (*v*), infundibulum (*i*) and a small bit of dura mater (*d*) adhering to the cerebellum. The darker areas in the top and bottom specimens are at places where the sections are thicker because of uneven cutting, and are not blue in the original.

In this and succeeding photographs, the top specimen is nearest the midline, the next below is the next laterally, and so on.

Forebrain: Grade 2 staining is limited to the mesial portions of the second and third temporal convolutions and, slightly more intense, to the uncinate gyrus. Just anterior and lateral to the exit of the optic nerve and below the anterior commissure an area of intense blue, about 1 by 2 mm., is probably the parolfactory area.

Corpus striatum is unstained except in one area about 6 by 2 mm. of very intense blue just above the descending cornu of the ventricle which occupies the position of the tail of the caudate nucleus and the amygdaloid nucleus.

Fig. 2.—Five days' incubation, monkey 9, first stage. This animal had a slower rate of invasion than the four-day monkey (No. 24). That the first stage of reaction is represented here is shown by the fact that the olfactory bulb (*o*) is stained, and the remainder of the central nervous tissues is unstained.

Interbrain: The thalamus shows Grades 2 and 3 staining of the mesial, anterior, and lateral nuclei. Grade 1 staining is seen in the hypothalamic area (corpora mammillaria). The pulvinar is unstained.

Midbrain: The red nucleus is unstained. The corpora quadrigemina show Grade 1 staining. A narrow band of Grade 2 staining is seen just above the pons in the region of the substantia nigra.

Pons Varolii: Grade 4 staining, the most intense in the entire specimen, is seen in the ventral gray matter of the pons (nuclei pontis) over an area measuring 3 by 7 mm. extending from the midbrain level nearly to the medulla, and from a plane slightly lateral to the midline to or almost to the lateral boundaries of the pons. Dorsally, a narrow band of Grade 2 staining extends through the tegmental

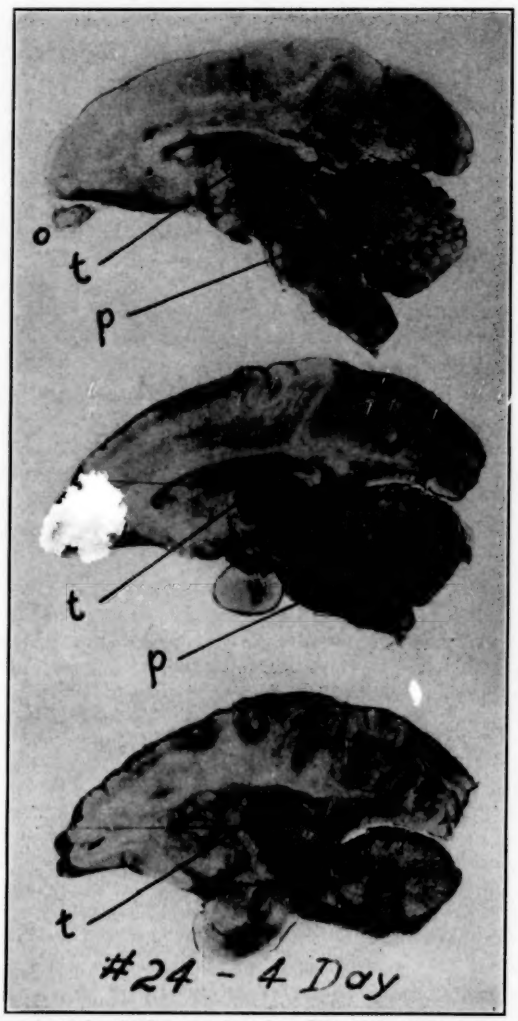

Fig. 3.—Four days' incubation, monkey 24. The dark areas are very deep blue. The olfactory bulb (*o*) in the original is bluer than the photograph shows. Note the particularly dense staining in the thalamus (*t*) and ventral region of the pons (*p*). The cerebral and cerebellar cortex is unstained.

region from the midbrain (continuous with the band of the substantia nigra) down to, and including, the floor of the fourth ventricle, and this is probably the formatio reticularis.

Medulla: Staining is less intense than in the pons. Besides the stained formatio reticularis just mentioned, there is an area of grade 1-2 staining about 1 by 5 mm. long and about 1 mm. inside the ventral margin in the region of the olivary body. The rest of the medulla is unstained.

Cerebellum: No blue staining.

Spinal Cord: No blue staining is visible anywhere in the gray or white matter of the cord. The dural covering of the roots and dorsal ganglia is intensely stained.

Microscopic Examination.—Olfactory Bulb: Throughout the substance and particularly in the glomerular and next two subjacent layers there is an enormous increase in the microglial (rod) cells. In the mitral cell layer these are clumped in places, suggesting neuronophagia, but a careful search failed to reveal degenerating nerve cells within the clumps. No nerve cells could, however, be found in any of the sections: whether they had entirely disappeared or were merely overlaid by the heavy infiltration of microglia could not be determined. In the pial meshes there is a heavy infiltration with lymphocytes and polymorphonuclear leucocytes, and some lymphocytes were also found scattered in the substance of the bulb.

Thalamus: There is marked capillary dilatation throughout. No perivascular infiltrations, no increase in microglia, no degenerated nerve cells are seen.

Cerebral Cortex: Some capillary dilatation but no other changes in the substance, meninges, or vessels are noted.

Pons (Ventral Region): There is conspicuous increase in the rod cells throughout the gray matter, also very marked dilatation of the capillary bed. The nerve cells appear normal. There are no perivascular or meningeal infiltrations.

Medulla: No changes are apparent other than a slight or doubtful increase in the rod cells.

Spinal Cord: No abnormalities are noted.

Summary.—Selective localizations of trypan blue staining were in the olfactory bulbs, olfactory areas of the forebrain, thalamus, pons and (slight) in the medulla. There were no localizations in the remainder of the cerebral cortex, in the cerebellum, or in the spinal cord. Microscopic changes were seen in the olfactory bulb, in which they are more advanced than elsewhere, in the thalamus, and in the ventral region of the pons. Invasion by rod cells (microglia) is notable.

Five Days' Incubation.—Monkey 9, inoculated intranasally on July 17, 1936, behaved normally throughout experiment. Temperatures were as follows: July 18, 101.0° F.; July 21, 101.7° F.; July 22, 103.4° F. On July 21, trypan blue solution was given intramuscularly; July 22, 9 A.M., 25 c.c. trypan blue was given intraperitoneally, and at 1 P.M., 10 c.c., intravenously. At 4 P.M. the monkey was killed by exsanguination under ether anesthesia; 10 per cent neutral formalin solution was injected in the carotids.

Macroscopic Appearance.—The dura, choroid plexuses, velum interpositum, and infundibulum show the usual deep blue staining. Both olfactory bulbs in their rostral halves show streaks of Grade 2-3 of blue staining. None of the other portions of the brain or spinal cord substance shows any staining at all, with the possible exception of the amygdaloid nucleus in which a very faint bluish tinge is barely visible. The specimen is unusually good in that it shows none of the greenish tint seen in several of the other specimens in unaffected areas, which is probably due to toxic effects of the dye itself.

Microscopic Examination.—Olfactory Bulb: Moderate capillary dilatation is seen in several places. There are a few areas in and near the glomerular layer which show a distinct increase of microglial cells. Meningeal infiltration is absent. The nerve cells appear normal.

The tissues from other portions of the central nervous system appear entirely normal.

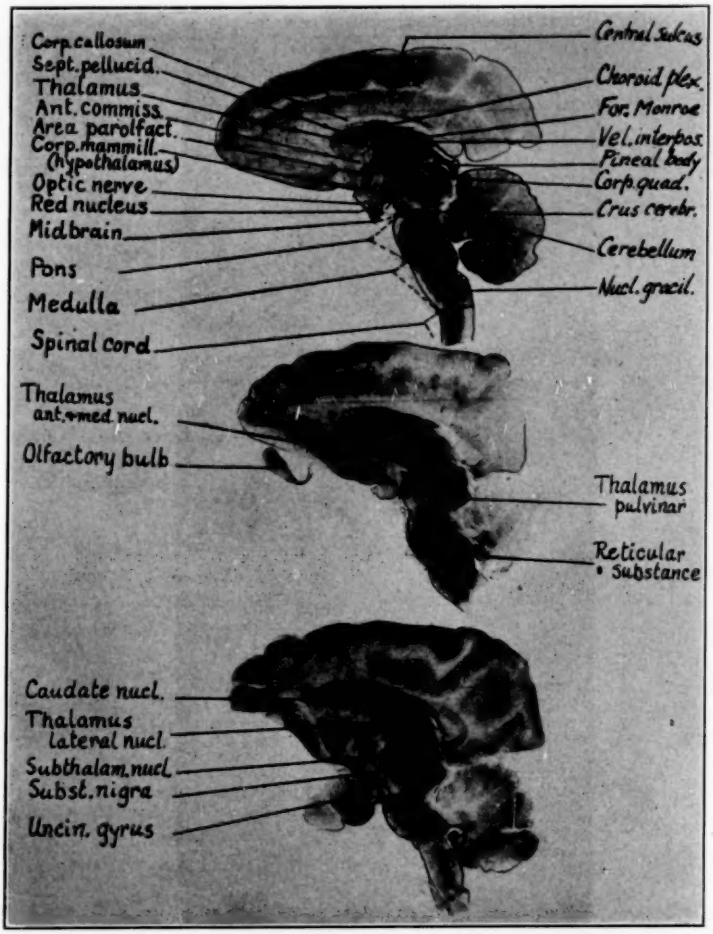

Fig. 4.—Six days' incubation, monkey 3, third stage. Intense staining in the brain stem and cervical cord. The legend on this and the succeeding specimen may be used as an anatomic guide to the other specimens as well. The contrast between the stained and unstained areas is particularly sharp.

Summary.—Lesions are limited to the olfactory bulbs, where they are slight, in an animal with a slower than average rate of invasion.

SIX DAYS' INCUBATION.—Monkey 3 was inoculated intranasally Nov. 13, 1935. Temperatures were not taken. No paralysis had occurred up to time of death.

On November 18, trypan blue solution was given intramuscularly and on November 19, trypan blue was given intravenously at 4:30 P.M. At 6:30 P.M. the animal was killed.

Macroscopic Appearance.—The staining is somewhat lighter than in No. 24; the gray matter outside the areas of positive reaction showing only a very faint greenish color.

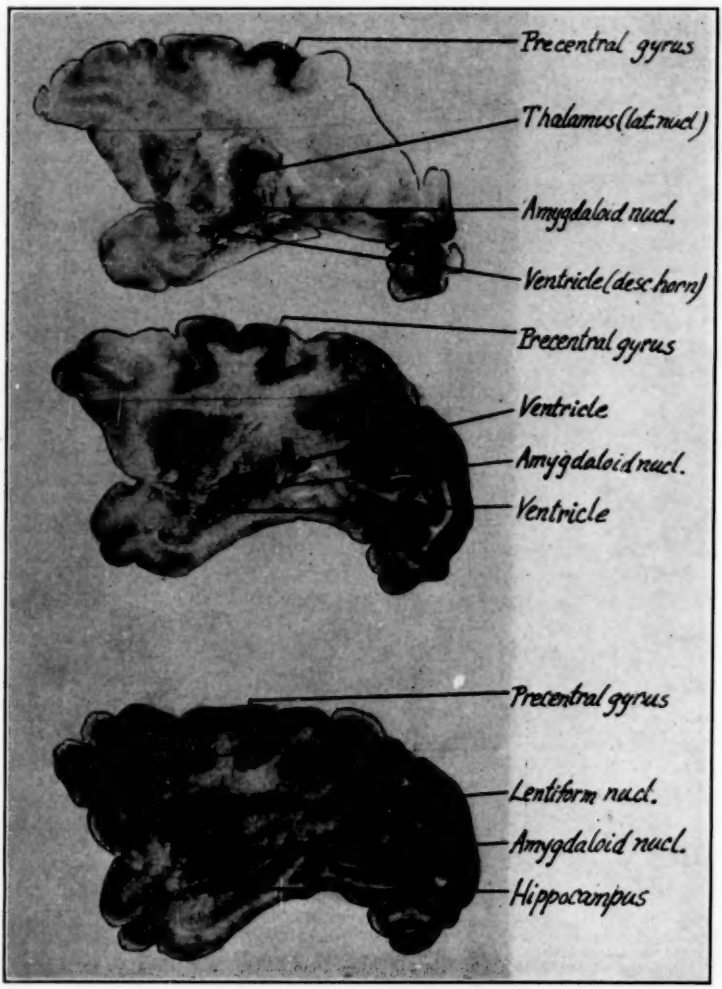

Fig. 5.—Six days' incubation, monkey 3. These sections are just lateral to those of Fig. 4. The amygdaloid nucleus (perhaps including the tail of the caudate nucleus) is deep blue. The lentiform nucleus, though appearing dark in the photograph, is not stained blue in the original. Marked staining is seen in two areas of the cerebral cortex, the precentral gyrus and the hippocampus (uncinate gyrus). This is the only specimen in which any considerable staining was found in the cerebral cortex outside of the uncinate gyrus.

Olfactory Bulbs: No staining.

Forebrain: No bluish staining excepting in the precentral gyrus on the convexity which shows Grade 2 staining and the uncinate gyrus (Grade 2).

Corpus Striatum: Unstained excepting an area about 2 by 6 mm. just above the descending horn of the lateral ventricle, in the position of the tail of the caudate nucleus and the amygdaloid nucleus (Grade 2-3). The same area was stained in No. 24.

Interbrain: The mesial, anterior, and lateral nuclei and also the pulvinar of the thalamus show Grade 3 staining. The corpora mammillaria show Grade 1 staining.

Midbrain: The red nucleus and corpora quadrigemina show Grade 2-3. No staining is seen in the region of the substantia nigra.

Pons Varolii: The ventral gray matter shows Grade 2-3 staining, and Grade 1-2 also shows in the dorsal portions in continuity with a rather diffuse area in the mesial portions of the medulla. The staining in the pons thus is somewhat more extensive than in No. 24.

Medulla: In the mesial portion the gray matter is rather diffusely stained (Grade 2-3). In the more lateral portions the stain is more localized in the portions below the floor of the fourth ventricle, but scattered small areas of blue (Grade 1-2) are seen throughout the substance. The staining in the medulla is more extensive than in No. 24.

Cerebellum: No staining.

Spinal Cord: In the cervical region the gray matter is intensely stained, with a distinct difference between the two lateral halves, one being Grade 3 and the other Grade 4. The posterior horns, the intermediate portions, and the anterior horns are almost equally blue. The white substance shows no visible staining. The thoracic portion is also well stained, and the lumbar region, while blue (Grade 2), is much less intensely stained than the cervical and thoracic segments. In longitudinal sections the dye is seen to be unevenly distributed at different levels.

Microscopic Examination.—Olfactory Bulbs: Throughout the nerve substance and in the pial meshes there is a notable infiltration with lymphocytes and a few polymorphonuclear leucocytes; and one perivascular cuff is seen. There is also a marked increase in the microglial (rod) cells with several small focal accumulations. No neuronophagia was found after careful search. The mitral cells show clear outlines in protoplasm and nucleus, and the nucleoli are centrally placed. The capillary bed is not conspicuously dilated, which may explain why macroscopic staining is not present.

Cerebral Cortex (frontal): No changes are seen except slight hyperemia.

Amygdaloid Nucleus: Slight capillary hyperemia and a slight or doubtful increase in the microglial cells are the only changes found.

Uncinate Gyrus: Moderate capillary dilatation is present, and also a few lymphocytes and polymorphonuclear cells are found in the pial meshes.

Choroid plexus and *ependyma* are entirely normal.

Thalamus: Marked capillary dilatation is present, the plasma appearing bluish in sections without counterstain and many of the capillary endothelial nuclei showing a deep blue color. In several places there are foci of rod cells. Cuffing, which is slight, is seen around one small vessel.

Medulla: The changes here are marked and relatively advanced in the gray matter, though slight or negligible in the meninges. Several degenerated nerve cells are surrounded and overlaid with rod cells; lymphocytes and a few polynuclear leucocytes are seen. Many clumps of microglial cells are seen. Several small vessels with moderate, but not deep, perivascular infiltrations are present. Several nerve cells with intranuclear inclusions are found, the only instance in the series of experiments. A few nerve cells are stained by trypan blue. Marked capillary dilatation is present.

Cerebellum: No notable abnormalities are found.

Spinal Cord: In striking contrast to other portions of the central nervous system, the ganglion cells contain considerable amounts of trypan blue, especially in the nuclei which are quite densely stained. This is much more marked in the cervical and upper thoracic than in the lumbar levels. The majority of stained

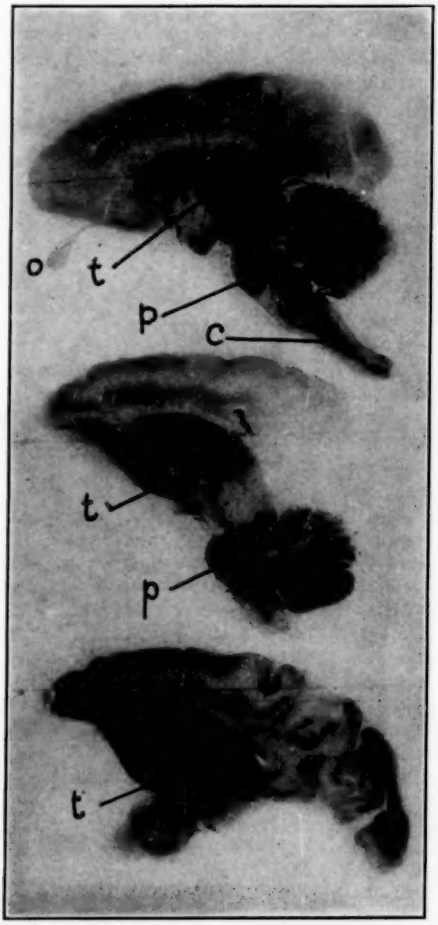

Fig. 6.—Seven days' incubation, monkey 4. The thalamus (*t*) is deeply stained, and lighter staining is seen in the ventral area of the pons (*p*) and in the cervical cord (*c*). The olfactory bulb (*o*) is unstained. The cerebral cortex is unstained.

cells are in the anterior half of the gray matter, but scattered stained cells are seen also in the mid-portion and a few in the posterior horns. In the cervical level the nerve cells stain very poorly, and the Nissl substance has disappeared; there are dense patches of microglial infiltration, some of which may represent neurophagia, although nerve cells were not found within them; there are slight infiltration of lymphocytes and a few polymorphonuclear leucocytes in the anterior fissure and

slight cuffing of one small vessel. In the thoracic cord the nerve cells stain poorly; there is heavy rod cell infiltration in the gray matter but no meningeal or perivascular infiltration. In the midlumbar level the contrast with the upper levels is sharp; the nerve cells stain excellently and show normal appearance, with well-stained and normally distributed Nissl substance; no rod cell aggregations or increase and no meningeal or perivascular infiltrations are seen. Apart from a fairly marked dilatation of the capillary bed, the changes in the supporting tissues,

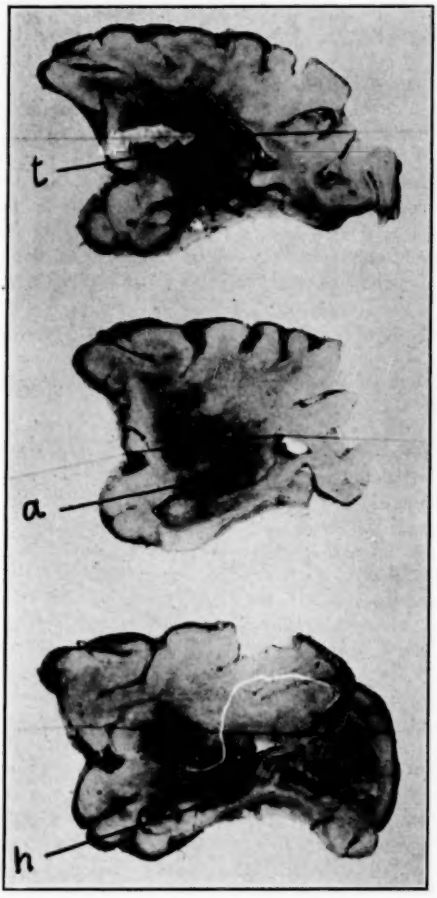

Fig. 7.—Seven days' incubation, monkey 4. Sections lateral to those of preceding photograph (Fig. 6). Localizations of dye in the thalamus (lateral nucleus) (*t*), amygdaloid nucleus (*a*), and uncinate gyrus (*h*) are conspicuous.

white matter, larger vessels, and meninges are very slight. No intranuclear inclusions are found. The picture as a whole is of a primary insult in the nerve cells, which permits dye to pass through the membranes both of the outer protoplasm and of the nucleus.

Summary.—The olfactory bulbs show microscopic abnormalities but no gross staining. Selective localizations of trypan blue are present and marked in the

uncinate gyrus, amygdaloid nucleus, thalamus, midbrain, pons, medulla, and spinal cord. Evidences of nerve degeneration are advanced in the medulla and in the gray matter of the cord, especially in its upper portions. It is evident that this animal had a heavier than average infection and would have become paralyzed very shortly.

SEVEN DAYS' INCUBATION (TWO SPECIMENS).—Monkey 4 was inoculated Nov. 13, 1935. No temperatures were taken. Paralysis did not occur up to time of death. Dye was injected intramuscularly on November 19, and intravenously on November 20. The animal was killed on November 20, about two hours after the last dye injection.

Macroscopic Appearance.—Olfactory Bulbs: No staining.

Forebrain: No stain is found anywhere except in the uncinate gyrus, where it is quite intense (Grade 3-4).

Corpus Striatum: A small area of Grade 3 staining is seen in caudate nucleus just above the thalamus, and again in the tail of this nucleus and the amygdaloid nucleus above the descending cornu of the lateral ventricle in the same area which was found stained in previous specimens.

Interbrain: The mesial, anterior, and lateral nuclei of the thalamus are blue (Grade 3), but the pulvinar is not. The mammillary bodies (hypothalamus) are not stained.

Midbrain: A small area of blue, Grade 2, is seen in the region of the red nucleus.

Pons: The ventral region shows staining, Grade 2, in the same area noted in previous specimens.

Medulla: Very little stain is visible between the pons and the level of the cuneate tubercle, where in the central portions and in continuity with the gray matter of the cervical cord Grade 2 staining is seen.

Cerebellum: No staining.

Cervical Cord: In the uppermost portion, one side of the gray matter shows Grade 2 stain, most marked in the anterior horn. No stain is seen in the remainder of the cervical cord, nor in the thoracic and lumbar regions.

Microscopic Appearance.—Left Olfactory Bulb: There is a diffuse, and in places very marked, microglial infiltration especially marked in the glomerular, subglomerular, and central layers. There is also a fairly marked capillary dilatation. One pial vein shows a moderate perivascular infiltration with lymphocytes and a few polymorphonuclears. In the substance cuffing of a small vessel is seen. The pial infiltration is only slight. The nerve cells are fairly numerous and probably normal, although the fixation of the specimen as a whole is imperfect.

No other portions of the central nervous system were examined microscopically.

Summary.—There are localizations in the upper brain stem and olfactory cortex and in the upper part of the spinal cord. The specimens give the impression of a relatively mild infection with beginning invasion of the cord.

MONKEY 13 was inoculated Aug. 4, 1936. On August 6, the animal appeared "nervous"; August 7, nervous and irritable with temperature of 104.4° F.; and on August 8, nervous and irritable with temperature of 105.2° F. Same condition continued on August 9; temperature, 105.0° F. August 10, dye was injected intramuscularly. On August 11 symptoms were nervousness, fine tremors, weakness of legs; temperature, 104.4° F. Dye was given intravenously at 1:15 P.M., and the specimen was killed at 4:15 P.M.

Macroscopic Appearance.—Olfactory Bulb: Heavy staining, about Grade 4.

Forebrain: No staining is found, except very faint (Grade 1) in uncinate gyrus, especially at the tip (uncus).

Corpus Striatum: No staining except in same area as in previous specimens in roof of descending horn of ventricle (tail of caudate and amygdaloid nucleus) where it is Grade 2.

Interbrain: The staining is rather faint (Grade 1-2) and is seen in the anterior and lateral nuclei. The mammillary bodies are unstained.

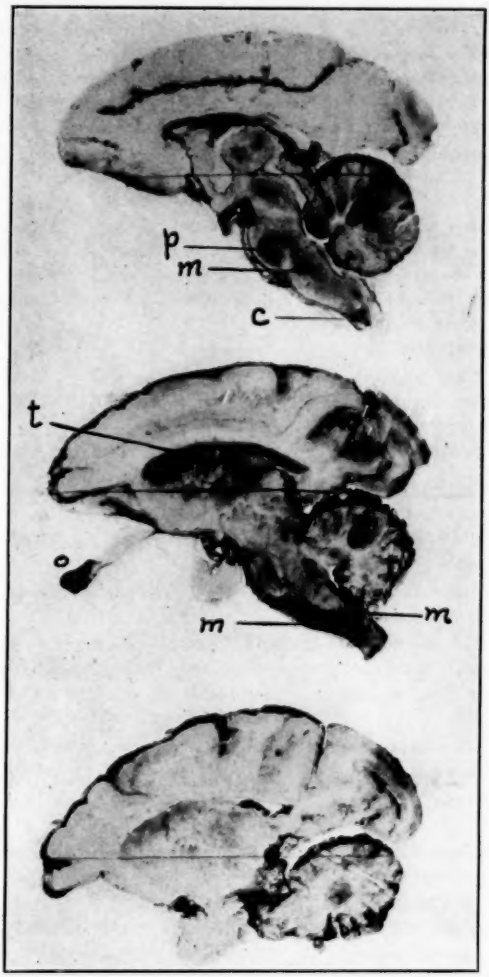

Fig. 8.—Seven days' incubation, monkey 13. The olfactory bulb (*o*) is rather deeply stained. There is faint staining in the thalamus (*t*). The chief involvement appears to be in the pons (*p*) and medulla (*m*) and in the cervical cord (*c*). The cerebral cortex and cerebellum are unstained. The cervical cord below the section is quite heavily stained.

Midbrain: Grade 1 staining appears in the region of the red nucleus.

Pons: The ventral area shows streaks of Grade 2 staining, and there are also a few spots in the dorsal region.

Medulla: Small spots of intense stain are seen in the ventral region at about the level of the pyramid. In the central region just below the pons an area of somewhat more diffuse stain, Grade 2, is seen.

Cerebellum: No staining.

Spinal Cord: By contrast with the brain, the staining in the cord is intense, especially in the cervical region where the gray matter, both anterior and posterior, is Grade 4. The gray matter of the thoracic cord is also deeply stained. In the lumbar cord, in one section, one of the anterior horns is deep blue (Grade 4), while the other is lightly stained (Grade 2). In longitudinal sections, some unevenness of staining is apparent at different levels, but the stain in the cervical region throughout is very much more intense than in the thoracic and lumbar levels.

Microscopic Examination.—Right Olfactory Bulb: The sections are thick, making it difficult to find mitral cells. There is an enormous infiltration with microglia in the glomerular and subjacent layer, extending into the granular layer. In the pia a fairly heavy infiltration with lymphocytes and some polymorphonuclears is found in places. Some cuffing of veins in the substance of the bulb is also found. The nerve cells are difficult to locate, being covered by heavy layers of oligodendroglia; the few that were found appear normal. It is impossible to determine whether or not neuronophagia is present.

No other sections from this animal were examined.

Summary.—There is selective staining in the brain stem, olfactory bulb, and spinal cord. The relative intensities of stain give the impression of a subsiding reaction in the brain stem and a much more active and severe reaction in the cord. The reaction in the olfactory bulb appears to be still very active.

NINE DAYS' INCUBATION.—Monkey 2 was inoculated Oct. 22, 1935. No temperature record was taken. Dye was injected intramuscularly on October 30, and intravenously on October 31, at 2 P.M. The specimen was killed at 5 P.M. No paralysis occurred.

Macroscopic Appearance.—Olfactory Bulbs: The right bulb is unstained; the left shows Grade 2 staining.

Forebrain: There is no staining anywhere, even in the uncinate gyrus.

Corpus Striatum: No staining appears except in the gray matter in the roof of the descending horn (tail of caudate nucleus and amygdaloid nucleus), where it is Grade 1-2.

Interbrain: The stain is rather faint (Grade 1-2) and diffuse, being seen mainly in lateral and posterior nuclei.

Midbrain: Grade 1-2 staining appears in the region of the red nucleus and substantia nigra.

Pons: There is Grade 2 staining in the dorsal portions, but none in the ventral area which was so well stained in the earlier specimens. The stained area in the pons is continuous with that in the medulla.

Medulla: Rather diffuse Grade 2-3 staining appears, especially conspicuous in the floor of the fourth ventricle and extending through the central portions to about 1 mm. from the ventral surface and from the level of the pons to the lower level of the pyramid. The region of the cuneate nucleus is unstained.

Spinal Cord: In the uppermost portion and again in the middle portion of the cervical cord, a deep blue area, rather sharply limited, of staining (Grade 3-4) is seen in the gray matter, involving both horns. The thoracic and lumbar regions are unstained.

Microscopic Appearance.—Left Olfactory Bulb: There is a notable increase in microglial cells, especially in the glomerular and subglomerular layers. Several

moderate perivascular infiltrations are seen, and the pial meshes show a moderate infiltration with small round cells and polymorphonuclears. The nerve cells are numerous and apparently normal. In a few places the rod cells occur in clumps, which may represent neuronophagia, but no degenerating nerve cells are seen among them.

Fig. 9.—Nine days' incubation, monkey 2. Staining here is entirely limited to the brain stem and is deepest in the pons and medulla.

Thalamus: There is moderate capillary dilatation. There are several patches of microglial infiltration, one quite large, but no definite neuronophagia. Moderate cuffing of a few veins is seen. The ependyma appears normal.

Medulla: The veins are distended and some of them show slight cuffing. There are several areas of marked rod cell infiltration, with a few small clumps suggestive of neuronophagia. The rod cells are also increased throughout the substance.

Cervical Cord: There is slight perivascular cuffing in one place but no meningeal infiltration. In the anterior horn one large and one small collection of rod cells

are seen; in the latter a degenerating nerve cell is visible. Several nerve cells look normal, but the majority stain poorly, without Nissl substance.

Thoracic Cord: The sections are small and unsatisfactory, but in one a small perivascular infiltration and a few small aggregations of rod cells are seen.

Lumbar Cord: In striking contrast with the cervical cord, the nerve cells stain well with normal Nissl substance. No perivascular or meningeal infiltrations nor aggregations of microglial cells are found.

Summary.—There is rather diffuse and light staining in the brain stem with less marked involvement of its uppermost portions than in previous specimens, and marked staining, rather sharply localized, in the midcervical cord. One olfactory bulb is stained; the other, unstained. The impression is that of a subsiding reaction in the brain stem, with discrete localized reaction in the cord, in an animal that might perhaps have survived the infection.

SUMMARY OF LOCALIZATIONS

These are shown in Table I. The control animal, No. 5, shows no visible staining with trypan blue. The small spot of blue in the subthalamic nucleus of the three-day animal, No. 6, is of doubtful and

TABLE I

	INCUBATION							
	CONTROL	3 DAYS	5 DAYS	4 DAYS	6 DAYS	7 DAYS		9 DAYS
	NO. 5	NO. 6	NO. 9	NO. 24	NO. 3	NO. 4	NO. 13	NO. 2
Olfactory bulb	0	0	++	+++	++*	0*	++++	0 right ++ left
Forebrain								
Precentral	0	0	0	0	++	0	0	0
Temporal	0	0	0	++	0	0	0	0
Uncinate	0	0	0	+++	++	+++	+	0
Corpus striatum								
Amygdaloid nucleus	0	±	±	+++	++	+++	++	++
Interbrain								
Thalamus								
Medial nuclei	0	0	0	++	+++	+++	+	0
Anterior nuclei	0	0	0	++	+++	+++	+	+
Lateral nuclei	0	0	0	++	+++	+++	+	+
Pulvinar	0	0	0		++	0	0	
Hypothalamus								
Corpora mammillaria	0	0	0	+	+	0	0	0
Subthalamic nucleus	0	+	0	0	0	0	0	±
Midbrain								
Red nucleus	0	0	0	0	++	++	+	+
Corpora quadrigemina	0	0	0	+	++	0	0	0
Substantia nigra	0	0	0	++	0	0	0	+
Cerebellum	0	0	0	0	0	0	0	0
Pons varolii								
Ventral region	0	0	0	++++	+++	++	+	0
Dorsal region	0	0	0	++	++	0	+	++
Medulla								
Ventral region	0	0	0	+	++	0	++	++
Dorsal region	0	0	0	+	++	0	++	++
Central	0	0	0	0	++	++	++	++
Cord								
Cervical	0	0	0	0	++++	++	++++	+++
Thoracic	0	0	0	0	+++	0	++++	0
Lumbar	0	0	0	0	++	0	+++	0

*No macroscopic staining, but marked histologic abnormalities.

perhaps negligible significance. The earliest stage of definite reaction in the central nervous system is shown in No. 9, killed on the fifth day after inoculation and a few hours after fever had begun, in which trypan blue staining is limited to the olfactory bulbs. Infection and invasion in this animal were a day or so slower in appearing than average, an example of the considerable variability so characteristic of poliomyelitis, both experimental and human.

The second stage is illustrated by No. 24, killed four days after inoculation, in which infection and invasion were rapid and severe. Here, the staining is extensive and intense but still limited to the areas of the central nervous system above the spinal cord, and is particularly marked in the olfactory bulbs and the brain stem above the medulla.

The third stage is illustrated by No. 3, killed six days after inoculation, in which the distribution in the brain stem is much like that in No. 24 (though more marked in the medulla), but the inflammatory change has now extended to the spinal cord where the upper (cervical) portions are more heavily stained than the lower. In this specimen for the first time definite degeneration of nerve cells is found, as shown by the normal microscopic signs and also by deposition of trypan blue in the cytoplasm and nucleus.

Specimens 4, 13, and 2, representing the seventh and ninth days, illustrate some of the later, preparalytic developments and variations, such as increasing involvement of the lower spinal segments, irregularities of distribution of lesions within the cord, and suggestions of subsidence of the inflammatory reaction in the olfactory bulbs and brain stem.

The experimental observations may be summarized as showing the progress of reaction to poliomyelitic infection during the incubation or preparalytic period as follows: (1) a primary stage of rhinencephalitis (olfactory bulbs only), succeeded by (2) a secondary stage of basal encephalitis, rather explosive in nature, consisting largely of hyperemia and microglial infiltration, succeeded by (3) a stage of myelitis with beginning nerve cell destruction, followed by (4) a stage of advancing and localizing myelitis simultaneous with beginning subsidence of the encephalitis.

The early and consistent involvement of the secondary olfactory centers (amygdaloid nucleus, uncinate gyrus) is of interest in relation to the olfactory route of invasion. The experiments as a whole give convincing evidence of the descending or caudad direction of poliomyelitic invasion into and through the central nervous system, after intranasal inoculation.

The nature of the inflammatory reactions in the early stages of infection is of considerable interest. That the localized areas of trypan blue staining are due to the presence of virus in those areas seems

reasonably assured by comparison with the previous series of experiments in which the localizations of virus were determined and by comparison with the absence of stained areas in the central nervous system in the uninoculated control. The correspondence between the localizations of dye and of abnormalities in the microscopic appearance is also reasonably good; although in a few places (for example, the olfactory bulbs in No. 6) histologic changes were present where trypan blue was not visible, and in some of the trypan blue stained areas, histologic changes were slight or doubtful. Under the microscope the trypan blue becomes difficult to see except in the spinal cord and occasionally in the medulla where it has invaded the nerve cells. In most other places its macroscopic visibility seems to depend upon dilatation of the capillary bed, in which a faint bluish tint of the plasma and occasionally a more marked staining of the endothelial nuclei can be detected. Hyperemia is familiar as one of the most constant and marked features of the central nervous tissues in poliomyelitis, and the present observations suggest that it is probably the first tissue response to the virus. In addition, the present observations corroborate the studies of Hurst[8] that invasion by the microglial (rod) cells is an early and characteristic feature of the pathologic histology of poliomyelitis. These cells, the "leucocytes of the central nervous system," not only constitute the principal element in areas of neuronophagia, but also are increased rather diffusely in infected areas before changes in nerve cells are manifest and can be found in the perivascular infiltrations.*

They are readily identified by the shape of their nuclei, which are pleomorphic and irregular in outline, usually with reentrant angles or curves such as are not seen in other glial cells. The cytoplasm is not seen except with special stains.

The present observations further confirm the contentions of Fairbrother and Hurst[11] that the perivascular and meningeal reactions are secondary phenomena; in most of the sections the meningeal infiltrations were either absent or slight in degree, even at times and in places when the parenchymal lesions were well advanced. Perivascular infiltrations (cuffing) were commoner than meningeal but were relatively slight.

In contrast with the report of Sabin and Olitsky,[13] neuronophagia in the olfactory bulbs was not identified with certainty in any of the specimens. This is not to say that it may not have been present. The mitral cells are bedded in a dense mass of small round glial cells

*I suspect that, if looked for, they would often be found in the cerebrospinal fluid in poliomyelitis and perhaps other virus diseases of the central nervous system. Fraser's description[9] seems quite characteristic of the microglial cell. Speaking of the cerebrospinal fluid in poliomyelitis he says: "In the more acute stages, larger cells with very irregular nuclei and a faintly basophilic and vacuolated cytoplasm were present in considerable numbers."

which conceal them in thick or heavily stained sections, and early degenerative changes are easily overlooked. In a few of the present specimens, clumps of microglial cells in or near the mitral cell layer may have concealed degenerated nerve cells within, but in no case were the latter seen. On the other hand, definite neuronophagia was found in the medulla and cord in some of the specimens, and manifest degeneration without neuronophagia was found in the cord in a few.

It seems correct to state that with the exception of necrosis of the nerve cells, the various tissue alterations described are of a reversible (recoverable) nature and that above the level of the medulla, nearly all the lesions noted in the present series were of that kind.

Finally, attention is directed to certain interesting features of the localizations of the spinal lesions in the seven- and nine-day animals. Thus, in No. 4 (seven-day incubation), dye was limited not only to a single level of the cord but to one lateral half of the anterior horn. In No. 13 (seven-day incubation), in which the distribution of trypan blue was much more extensive and intense in most places than in No. 4, there was a marked difference in the two lateral halves of the lumbar cord. In No. 2 (nine-day incubation) two separate areas in the cervical cord were stained while the rest of the cord was unstained. Differences in staining between the two lateral halves of the cord were also noted in No. 3. These observations may well be of importance as analogues of the varying and restricted sites of paralysis, so often one-sided, in man, thus illustrating the possibilities of variation in spinal localization after infection by the olfactory route.

DISCUSSION

The results of the present experiments on visualization of the evolution of poliomyelitic lesions during the period of invasion conform reasonably well, if not in all details, with the earlier series in which the localizations of the virus itself during the same period were determined. Both series bring out the following facts: (1) that both virus and lesions are first detected in, and limited to, the olfactory bulbs; (2) that both spread next to the basal regions of the central nervous system above the spinal cord; (3) that both are next found (sixth or seventh day after inoculation) in the spinal cord. Variations and discrepancies in time of localization amount to not more than one day, and the exact localizations differ only in minor details. The cerebral cortex, excepting the olfactory areas, contains no virus and shows only infrequent and mild lesions.

Both series of experiments also harmonize, I believe, with the pathologic process which probably occurs in human poliomyelitis during its early stages, consisting of a progressive, descending infection, with accompanying inflammatory reactions, of the central nerv-

ous system successively involving the olfactory bulb,* the brain stem and, in paralytic cases, the spinal cord. Indeed, it is difficult to account for the character and order of appearance of the clinical manifestations of acute poliomyelitis and even more difficult to explain the failure of paralysis to appear in the nonparalytic cases, in which the clinical manifestations (usually including abnormalities in the cerebrospinal fluid) are identical with the preparalytic manifestations in cases going on to paralysis, on any other basis than a descending infection which shows a strong tendency to halt at one point or another in its anatomic progress through the central nervous system. It is hard to conceive of a blood-borne infection acting in this way and, in particular, permitting the anterior horns of the cord, the most highly susceptible parts of the central nervous system to poliomyelitic virus, ever to escape. The fact that the cerebrospinal fluid does not contain virus does not harmonize with transport by the blood stream. Moreover, the fact that the meningeal and perivascular lesions of the disease are secondary to a primary infection of the nerve cells and, in severe cases, may even fail to appear in areas where nerve cells are already dead, has long been apparent from human material studied post mortem and has more recently been proved by the experiments of Fairbrother and Hurst.[11] There can be little, if any, question that the virus of poliomyelitis exerts its primary and characteristic effects exclusively on the nerve cells. The recent experiments on dermal infection[14] do not contradict this since no dermal lesions have been described, nor do they, in my opinion, disprove the theory of axonal transmission.

The considerable difficulty encountered in infecting monkeys by the blood stream has to be taken into consideration. Very large amounts of virus suspension injected directly into the blood stream

*The observations of L. W. Smith[12] on 56 human olfactory bulbs from fatal cases of poliomyelitis have repeatedly been cited as showing no or only minor and presumably insignificant abnormalities and hence as evidence against the nasal route of infection. Indeed, such is the conclusion drawn by Smith himself. His description, however, not only shows pathologic changes to be present but is in agreement with my own contention that the changes in the olfactory bulb are probably like those in other portions of the central nervous system above the level of the medulla (e.g., the thalamus), that is, of a mild and recoverable nature. Smith's statement is as follows: "Examination of fifty-six olfactory bulbs microscopically has shown a surprisingly small amount of pathologic change. *There has frequently been edema and congestion, harbingers of more extensive damage, but in less than a fourth of them do the characteristic cellular infiltrative changes, as seen in the ganglia and nerve roots, appear.* Either any inflammatory reaction in these organs is extremely short-lived, unlike the lesions of poliomyelitis elsewhere in the central nervous system, or the virus passes along these structures without leaving its identifying signature." [Italics added.]

The fact therefore seems established that abnormalities do occur frequently in the human olfactory bulbs, that even infiltrative changes occur not uncommonly (20 per cent?). The assumption that the mildness of the lesions points to another than the nasal route of entry seems to be quite gratuitous. Certainly the clinical evidence, as well as some pathologic evidence (see Harbitz and Scheel's observations[8] on two patients dying during the stage of repair) points very clearly to the existence of lesions, often widespread, in the central nervous system that subside without leaving residual effects. How else can the nonparalytic cases with nervous symptoms and characteristic changes in the cerebrospinal fluid be explained; or the recovery, partial or complete, that is so frequent in the paralytic cases?

Indeed, the changes noted by Smith in the olfactory bulbs are exactly what I have expected would be found.

are required and do not always succeed in breaking down the effective normal blood-brain barrier.[15] The human analogue to such experimental conditions is difficult to envisage. One would have to assume the existence of some extranervous tissue or organ in which the virus multiplied, and virus has been conspicuously absent when searched for in the extranervous tissues of man save in the nasopharynx and its regional lymph nodes. On the other hand, it has been recovered several times from the nasopharyngeal washings.[16, 17]

There seems to be no valid reason to assume that in "abortive" poliomyelitis, infection has not yet entered the central nervous system, simply because the cerebrospinal fluid shows no abnormalities.* Such abnormalities have been shown by Fairbrother and Hurst[11] to be secondary and subsequent to primary nerve tissue infection and to arise from drainage through the perivascular channels into the subarachnoid space of the products of inflammation, protein and cells, in the nervous parenchyma. The symptoms in the cases reported by Paul, Salinger, and Trask,[17] fever, vomiting, and headache, are the ordinary onset symptoms of poliomyelitis in general, such as are not uncommonly accompanied by abnormalities in the cerebrospinal fluid in nonparalytic and paralytic cases.

Objections to the gastrointestinal route are, to my mind, convincing. Experimentally, it has been clearly shown[19, 20] that when trauma to the tract and contact with the nasopharynx are avoided, virus, even in very large amounts, passes through it without causing infection and can even be recovered from the stools. The only successful experiments have depended either upon access to the nasopharynx or upon trauma to the tract. Since preceding trauma or infection or mechanical disorders of the bowel (such as volvulus, ulceration, etc.) are certainly of rare occurrence in man, the gastrointestinal portal can probably be dismissed as of little significance. The nasal portal remains the only one for which preceding trauma is not essential. The following comments are based on the thesis that it is the actual route of entry in man.

When poliomyelitic infection does enter the human body through the olfactory mucosa, it seems highly probable that it sets up in the central nervous system, as it has been shown to do in the monkey, a succession of inflammatory reactions which constitute the anatomic basis and source of the various clinical manifestations of the disease.

This concept is particularly illuminating in the interpretation of character and course of the onset and other early symptoms of poliomyelitis; of the so-called abortive and nonparalytic cases which form about 80 per cent of all recognizable poliomyelitic infections; and of

*Levinson[18] has shown from five cases of paralytic poliomyelitis that in the preparalytic stage with weakness already apparent the cerebrospinal fluid may show no increase of cells and only a slight increase of globulin. His review of the literature reveals the fact that the fluid in such cases is not infrequently entirely negative at a time when the central nervous system is unquestionably infected.

the usual absence of symptoms referable to the cerebral cortex (neopallium). We may envision the disease as one due to progressive invasion of nervous tissue by a virus which is not only neurotropic but, even within the nervous tissues themselves, exercises a rather striking degree of selectivity, being capable of producing only transient and recoverable lesions (hyperemia, cell infiltrations) in certain parts of the central nervous system (upper brain stem); destructive lesions (cell degeneration) in only a few (anterior horn cells, motor cells of the medulla); and slight lesions or none at all in others (cerebral cortex, cerebellum).

Furthermore, the conclusion is ineseapable that in many instances the virus implants itself for a brief time only and, after invading the olfactory bulb and sometimes the brain stem, dies out without reaching the vulnerable lower motor neurons. Such appears to be the process in abortive and nonparalytic cases. The possibility that infected nerve cells in poliomyelitis frequently recover is one to which too little attention has been paid. Indeed, clinical experience indicates that in a certain proportion of cases even the vulnerable lower motor neurons recover from infection, since in nonfatal cases patients quite regularly regain part and sometimes all of the muscular strength lost during the acute stages of the disease.

The symptomatology of the disease shows an order of progression corresponding with the advancing distribution of lesions, and may, I believe, be properly divided into three main phases. The first phase is manifested by fever alone, and the lesions are confined to the olfactory bulb. The second consists of a symptom-complex in which more or less generalized affective, sensory, and autonomic phenomena are conspicuous, and the lesions consist mainly of a basal encephalitis without involvement of the spinal cord. During the third phase, in which lesions are now present in the spinal cord, there occur, usually in rapid succession, two kinds of symptoms: (a) localized autonomic and sensory phenomena arising in the lateral and posterior horns and dorsal root ganglia and (b) localized motor phenomena arising in the anterior horns. *The advance of infection may cease at any of the phases short of flaccid paralysis and place the case in the subclinical, abortive, or nonparalytic category.* The classification is given in greater detail in Table II.

The relationship of the various symptoms to their probable anatomic sources in the central nervous system has been discussed in considerable detail in another paper and need not be repeated here. With regard to fever, however, it now appears likely from the data in experiment 9 of the present series and from the recent experiments of Howe and Ecke[21] that this symptom, which is the earliest and most constant in poliomyelitis, may have its origin in infection of the

TABLE II

PHASE	SITE OF VIRUS AND LESION	SYMPTOMS	CEREBRO-SPINAL FLUID	CLASSIFICATION WHEN PROCESS FAILS TO ADVANCE BEYOND GIVEN PHASE
1	Olfactory bulb	Fever only	?	Subclinical
2	Brain stem	Fever, vomiting, headache, general hyperesthesia, drowsiness alternating with irritability, malaise, apprehensiveness	a) 0	Abortive
			b) +*	Nonparalytic
3a	Posterior and lateral horns and dorsal ganglia of spinal cord	Localized pains and tenderness, localized sweating, spine sign, painful Kernig	+	Preparalytic
3b	Anterior horns	Tremor,† weakness, flaccid paralysis	+	Paralytic

*Pleocytosis, increased protein. Negative fluid does not indicate that infection has not yet reached the central nervous system.

†Tremor may in some instances be due to involvement of the red nucleus.

olfactory bulbs alone and not primarily, as was previously suggested, in involvement of the hypothalamic centers. The affective and sensory disturbances of the second phase are reasonably referable to the diencephalon; and the autonomic disturbances to the base of the diencephalon, where, as Bard[22] states, there is a "dominant mechanism . . . capable of causing a simultaneous discharge over the entire series of preganglionic neurones." The functional disturbances of the bladder (retention) and of the gastrointestinal tract (constipation, occasional diarrhea) may also be due to disturbances in the higher autonomic centers. The preganglionic neurones have their origin in the lateral horns of the thoracic and lumbar segments. The origin of the localized autonomic disturbances of the third phase would seem to be here, just as that of the localized sensory and motor phenomena must be in the posterior horns and dorsal ganglia, and the anterior horns, respectively.

The speed of evolution, as well as the order of evolution of symptoms in man may quite reasonably be analogous to the speed and order of evolution of lesions in the experiments. The order seems to be quite regularly from above downwards, but the speed varies greatly. Thus in No. 9 only the olfactory bulbs showed lesions, and these mild, on the fifth day, while in No. 24 both the extent and severity of the lesions were vastly greater on the fourth. The extent and severity of the spinal lesions were more marked in No. 3 on the sixth day than in No. 2 on the ninth. The marked variations in the experiments obviously have their counterpart in the human disease which is so characteristically variable in the extent and severity of

symptoms, and also in the period of time over which they develop. A survey of any well documented series of cases of some size will bear this out. For example, in Draper's series[1] the majority of paralytic cases showed weakness or paralysis within two or three days of the onset, some within a few hours and some within several days. In one case paralysis occurred eleven days after the onset. In a considerable number (dromedary cases) there was an interval, in one case of eight days, of symptomatic silence between the initial stage and the paralytic stage. Finally, as is true in all epidemics, a large proportion showed only the initial stages and developed no paralysis at all. Thus, the disease may run a slow course, a mild course, or a fulminant and explosive course. In practically all cases, however, the symptoms and signs of the onset are similar and do not point to implication of the cord.

SUMMARY

1. Intravital staining with trypan blue of monkeys intranasally inoculated with poliomyelitis virus gives selective staining in the central nervous system of areas of gray matter corresponding with those in which virus has previously been found to be present—particularly in the olfactory bulb and olfactory areas of the cortex and of the corpus striatum, in the brain stem, and spinal cord.

The localizations of the dye are due largely to capillary dilatation of the capillary bed and partly to staining of tissue cells (endothelium of capillaries) and, in the medulla and cord, to staining of the nerve cells themselves. It is assumed that the capillary hyperemia is the first response to invasion of nerve cells with virus after the latter has reached the critical concentration necessary to affect the cellular metabolism.

2. By sacrificing animals, intravitally stained, on various days of the preparalytic period, the order of appearance and the descending progress of the lesions can be followed.

3. The first stage consists of lesions limited to the olfactory bulb and is accompanied by fever.

4. The second stage consists of a marked and extensive reaction in the brain stem down to the medulla, with implication of the secondary olfactory centers (amygdaloid nucleus, uncinate gyrus).

5. The third stage consists of an increased involvement of the medulla and beginning implication of the spinal cord.

6. Later stages show localization in restricted areas in the cord itself, sometimes unilateral, with beginning subsidence of the reactions in the brain stem.

7. No significant variations were found in the *order* of development of the lesions, but conspicuous variations occurred in their *speed of evolution*, their extent, and severity and in their localizations in the cord.

8. The present experiments suggest that, since the host cells for poliomyelitis virus are in all probability nerve cells, and since nerve cell degeneration in most of the areas manifestly invaded above the level of the medulla was conspicuously slight or absent, these cells must in many instances be invaded by virus without undergoing destruction and are therefore capable of full recovery. This principle is probably true even in the highly susceptible anterior horns of the cord and may account not only for the nonparalytic cases but also for the recovery, partial or complete, of the many patients with paralysis.

9. Reasons are discussed for believing that the present experiments can fairly be applied to human poliomyelitis; that inflammatory reactions in the brain stem occur in the brain stem in nonparalytic cases and in the preparalytic stage of paralytic cases, and that they are responsible for the initial and other early symptoms which are constant in recognizable cases of the disease.

10. It is not necessary or correct to postulate a preliminary period of "systemic," "general," or extranervous infection. The concept of poliomyelitis as a primary disease of the central nervous system is reaffirmed.

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FUTURE OF CHEMOPROPHYLAXIS AS A MEASURE FOR THE PRACTICAL CONTROL OF POLIOMYELITIS

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THE thought that certain chemical agents might serve to prevent the implantation of poliomyelitis virus at the portal of entry is not new. Soon after it was discovered that this disease could be transmitted to monkeys by the intranasal application of virus, Levaditi and Danulesco (1912)[1] attempted to prevent infection by first treating the nasal mucosa with chemical agents. However, the agents employed by them were chosen for their virucidal action rather than for their power to modify the permeability of the portal of entry and included such substances as potassium permanganate, hydrogen peroxide, phenol, menthol, iodine, and immune serum. Among those which were tested, potassium permanganate (1:500) protected two out of three monkeys, and one of five monkeys escaped infection in the iodine-treated group. Eight years later Flexner and Amoss (1920)[2] carried out similar experiments with chloramine T and dichloramine T, in both instances with negative results.

Present interest in chemoprophylaxis may be said to date from the observations by Olitsky and Cox[3] in 1934, who found that tannic acid instilled intranasally in mice protected a large percentage of animals against the virus of equine encephalomyelitis instilled intranasally four days later. In 1935 Armstrong[4] reported that a 3 per cent solution of alum protected mice against the virus of St. Louis encephalitis instilled intranasally several days later.

We are indebted to Armstrong and Harrison[5] for reviving interest in the possibilities of chemical prophylaxis in poliomyelitis. In May, 1935, they reported that a 4 per cent solution of alum applied intranasally conferred on monkeys a temporary resistance to virus instilled intranasally. Later, similar results were obtained with picric acid and with a combination of picric acid and alum.[6] These observations naturally suggested the practical possibilities of a chemical approach in the control of this disease; this became more apparent following the observations by Sabin, Olitsky and Cox (1936),[7] and by ourselves (1936),[8] which indicated that the protection afforded by chemical treatment may in some instances persist for months. It was this rather lasting effect which encouraged us to make a fairly comprehensive inquiry into the practical possibilities afforded by chemical prophylaxis.

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Our attention was directed to the possible use of chemical agents in the control of this disease early in 1935 after we had been engaged in an extensive search for evidence that immune serum and vaccines really afford significant protection against this disease.[9] This shift was prompted largely by a realization that its practical control would not be possible by such orthodox measures.

After preliminary tests with tannic acid, which yielded equivocal results, it occurred to us that such substances as picric acid and mercurochrome, because of their staining action, might modify the permeability of the olfactory mucosa, including the olfactory cells and hairs. Our first report dealt with the protective action of these two substances. This report appeared almost simultaneously with that of Armstrong and Harrison on picric acid. The observations presented in these two papers were in harmony so far as the results could be compared. Those obtained by the Eastern workers applied to the protection afforded a few days following the period of treatment, while our observations extended over periods of more than a month. What came as a real surprise in this early work was the duration of the protection afforded—a point which still remains unexplained.

With this as a background, we set out on an extensive study to determine the range of substances which are able to produce more lasting protection. Many chemical substances have been tested under more and more exacting conditions in an effort to elicit those possessing more outstanding protective powers. Instead of testing monkeys for resistance to infection several days to several weeks after treatment, we now follow the practice of waiting at least a full month before subjecting treated monkeys to virus instillations. The number of treatments have been reduced from three to five to one; and in carrying out the resistance tests, the intranasal instillations of virus are repeated until 100 per cent of an equal number of controls have succumbed.

Up to the present we have investigated more than fifty chemical agents. While most of these have been tested only in a limited way, others have been subjected to an extensive study. It is not my purpose to present the observations in detail. I have only time enough to say that a number of agents, some of them quite unrelated to each other, are protective and that among those which have been tested more fully, zinc sulfate solution seems to be the most effective. A 1 per cent solution of this agent thoroughly applied to the olfactory mucosa will protect about 90 per cent of monkeys a month later against virus instillations sufficiently heavy to infect 90 to 100 per cent of an approximately equal number of controls.

MODE OF ACTION

While we are not yet ready to express an opinion as to how chemicals may act to produce this protection, a few general remarks on this aspect of the subject may be of interest. My remarks, however, must be re-

garded as purely tentative since we are still quite unenlightened as to the precise mechanism underlying chemical protection. Besides, there is a possibility that different chemicals may confer protection by actions which differ from each other, and a given agent may act in more than one way. While this may be true, we feel certain that in no case does the type of resistance under discussion depend on a virus-destroying action, but rather on some effect on the portal modifying its permeability to the virus. How this permeability is influenced is not clear. While most of the protective agents are fairly acid and strong protein precipitants, there is no absolute correlation either between the power to precipitate egg white in solution and protective power, or between acidity and protecting power. For example, 1 per cent zinc sulfate, C. P., in distilled water (pH 5.9), is more protective than either 1 per cent tannic acid (pH 3.6), 1 per cent picric acid (pH 1.72), or 1 per cent uranium nitrate (pH 2.9), despite the fact that all three of the latter are more acid and are at least as good protein precipitants as zinc sulfate. While certain agents such as nickel sulfate (pH 3.2) and barium chloride (pH 8.0), possessing low protein-precipitating powers, also display low protective powers, it is possible to point to some agents which are highly protective and yet incapable of marked protein precipitation. For example, 1 per cent mercurochrome, which is alkaline in reaction (pH 8.8) and precipitates proteins only very slightly, if at all, is quite highly protective. Among the zinc compounds, 1 per cent solutions of zinc sulfate (pH 5.9), zinc chloride (pH 6.2), zinc bromide (pH 5.5), zinc acetate (pH 6.6), and zinc sulfocarbolate (pH 5.4) are all more or less protective; while 1 per cent zinc permanganate, which is very acid (pH 3.5) and a very strong protein precipitant, seemingly possesses little if any protecting powers.

In the case of zinc compounds, we feel that the protection may possibly depend on some union of the zinc ion with the protoplasm of the olfactory endings, a zinc proteinate being formed which is less permeable to the virus than the unmodified protoplasm. It is also possible that the protection may result from an actual destruction of the olfactory dendrites, possibly even of the olfactory cells themselves, and that the susceptibility returns only after these have been regenerated. Later in this paper I shall mention certain difficulties attending a satisfactory study of the anatomic effects produced by such chemical treatment.

PORTAL OF ENTRY

Any attempt to control poliomyelitis by devoting attention to the olfactory area should naturally be supported with good evidence that this is actually the region through which the virus gains admission to the body. It therefore seems proper that I should introduce this discussion with a review of the evidence concerning the olfactory area as the natural portal of entry. You may wonder why I stop to consider this

question in the face of the quite general recognition of the olfactory area as the sole natural portal. This widely held view, however, cannot yet be said to rest on unequivocal evidence. There are a few investigators who believe that in man the gastrointestinal tract is a more likely route of entrance, and recently it has been inferred that under natural conditions the virus may even enter through the skin.

Soon after the first successful transmission of the disease to monkeys by Landsteiner and Popper[10] in 1908, several investigators succeeded in infecting these animals by applying virus to the nasal mucosa. However, up to a few years ago the incidence of infection by this route was low, and little use was made of the intranasal method in experimental work. Recently, with a better technique and more virulent strains of virus, it has been possible to infect a high percentage of monkeys by this route. Establishment of the fact that infection can be easily induced in monkeys by the intranasal route further localized the problem as to through which portion of the nasal mucosa entrance is actually effected. Is it possible for the virus to pass through any portion, or does it pass through a restricted portion? As early as 1912, Flexner and Clark[11] made observations indicating that invasion may occur through the olfactory area. This was suggested by the fact that forty-eight hours after intranasal inoculation, virus was demonstrable in the olfactory bulbs, but not in the medulla and cord. This naturally raised the question, just how did the virus reach the bulbs? In 1917, Flexner and Amoss[12] made the following pertinent statement: "Having reached the upper respiratory mucosa, the virus may take either of two routes in invading the central nervous organs. It may penetrate first into the local blood vessels and be carried into the circulation and thence to the nervous tissue, or it may pass into the lymphatic vessels surrounding the olfactory nerves and ascend more directly to the brain, medulla, and spinal cord." The possibility that the virus may actually penetrate the nerve cell and be disseminated axonally, a view now widely held, was not considered, at least not seriously, at this time.

Before I go on with this discussion, I should like for the sake of clarity to review briefly the anatomy of the olfactory apparatus. In man the olfactory portion of the nasal mucous membrane occupies the upper third of the nasal septum, nearly the whole of the superior concha, and a small portion of the middle concha (Schaeffer, 1920, 1928).[13] In the healthy and fresh state, this area is demarcated from the adjacent mucosa by its yellowish or brownish tint and slightly greater thickness. Histologically, three kinds of cells may be recognized: (1) olfactory nerve cells, (2) supporting or sustentacular cells, and (3) small stellate basal cells. These cells rest directly on the tunica propria, without an intervening basement membrane. The supporting or sustentacular cells are tall, columnar cells, with oval nuclei. The superficial end of the cell extends a considerable distance peripheral to the nucleus and gives rise

to a superficial zone in the olfactory membrane which is practically devoid of nuclei. The deep-lying part of the cell is frequently forked, the processes ramifying with those of neighboring cells to form a sort of network. The small stellate basal cells lie within this network. These are pyramidal, cuboid, or round cells, which like the sustentacular cells present ovoid nuclei. They are regarded by some as additional and younger forms of supporting cells.

The olfactory nerve cells lie between the deep processes of the sustentacular cells. They are fusiform and bipolar cells with large spherical nuclei surrounded by a small zone of finely granular protoplasm. The nuclei of these cells are quite round and also larger than the nuclei of the sustentacular cells and are found for the most part below the zone of oval nuclei of the sustentacular cells. This cell has two processes: (1) The superficial process, or dendrite, is short and relatively thick, its actual length depending on the level of the cell within the mucosa. It courses through the nonnuclear zone of the epithelium and terminates slightly beyond the free surface of the epithelium in a small hemispherical or bulbous enlargement. This enlargement is surmounted by six to eight short cilia-like olfactory hairs, which project, often spinelike, from different parts of the rounded end. Occasionally the dendrite does not present this bulbous enlargement but itself projects spinelike and terminates in one or more hairs. (2) The deep process of the cell is threadlike from the beginning and is continued centrally as an axone. The axones from neighboring cells run together to form eventually about twenty nerve filaments which pass through as many openings in the cribriform plate to end finally in the glomeruli of the olfactory bulb. Each of the main filaments or branches of the nerve receives a tubular sheath from the dura and piarachnoid, the former being continued into the periosteum, the latter into the neurolemma of the nerve. Years ago Key and Retzius[14] concluded from experimental observations that the olfactory nerve filaments in the nasal mucosa are surrounded by a loose connective tissue with spaces continuous with those in the piarachnoid. More recently similar observations have been reported by other investigators, including W. E. LeGros Clark,[15] who has emphasized the role which these spaces play in the spread of septic processes from the nose to the meninges and brain. It was these spaces, which in reality are not "lymph spaces," which Flexner, no doubt, had in mind as the route by which the virus might pass to the central nervous system. But while there is evidence that bacteria and certain neurotropic viruses, such as that of equine encephalomyelitis (Rake,[16] 1937), may take this route, it seems quite unlikely from available evidence that this is the route actually taken by the virus of poliomyelitis.

In the olfactory bulb the deep processes or axones of the olfactory cells form a feltwork of interlacing fibers over the surface of the bulb lying in contact with the cribriform plate. Here they come in contact

with the bushlike dendritic processes of the large mitral cells, which constitute a part of the relatively superficial and circumferential zone of gray matter in the bulb. Peripheral to these cells in the gray matter are the smaller, less conspicuous tufted nerve cells, sharing in this relay. These two groups of nerve terminals—those coming from the olfactory cells on the one hand and those coming from the two kinds of nerve cells in the bulb on the other—give rise grossly to a circumscribed, more or less spherical thickening on the lower surface of the bulb, known as the olfactory glomerulus. Microscopically, this region presents a large number of small glomerular bodies containing the terminal arborizations of the respective processes. The axonal processes of the mitral cells go into the formation of the olfactory tracts, while those of the tufted cells pass through the anterior commissure to the opposite bulb.

In the gross the olfactory tracts are flat or triangular white bands which pass posteriorly on each side on the orbital surface of the frontal lobe to the so-called olfactory peduncle, located approximately at the level of the optic chiasma. Here the fibers diverge to form the lateral and medium striae and pass into substance of the cerebrum. It is unnecessary for our purpose to carry this anatomic description any farther.

In 1934 Brodie and Elvidge[17] and Gebhardt and myself[18] simultaneously reported the important observation that after the olfactory tracts have been cut, monkeys can no longer be infected by the intranasal route. This observation demonstrated for the first time the important fact that infection by the intranasal route under otherwise normal conditions can occur only through the olfactory portion of the nasal mucosa. This has been confirmed by Lennette and Hudson[19] (1935), who made the additional observation that the incidence of infection following the intravenous injection of virus is reduced some by a previous section of the olfactory tracts, suggesting that even when virus is introduced into the circulation, invasion of the central nervous system occurs more easily if the virus can enter from the olfactory mucosa. Armstrong[20] (1936) has reported that infection by the intravenous route occurs less easily in animals previously given intranasal treatments with picric acid. As further evidence, Sabin and Olitsky[21] (1937) have reported that monkeys infected by the intranasal route always show lesions in one or both bulbs, while those inoculated by other routes do not show these changes. A cellular infiltration was always observed in the outer layer of the bulb, which consists largely of olfactory nerve fibers, and also in the adjacent layer of glomeruli and in the underlying lamina granulosa externa and the lamina gelatinosa. We have been able to confirm these observations and have extended them some by tracing the infiltrative reactions from the olfactory mucosa to the olfactory bulbs. With a little experience it is possible in the monkey

to remove the olfactory mucosa, nerve filaments, and bulbs of both sides, all in one piece. A study of such material shows that the inflammatory reaction is also present in the smaller nerve bundles in the tunica propria and that these changes become more marked in the larger filaments approaching the bulbs.

While such observations as these exclude the probability that the virus passes readily through any portion of the nasal mucosa and definitely fixes the portal as the olfactory area, they do not wholly exclude the possibility that the virus may pass centrally by the way of the perineural spaces. But while this is true, I think that the perineural spaces as an important route can be almost entirely excluded on the basis of supplementary evidence pointing to the olfactory neurons themselves. A part of this evidence is presented by the fact that the virus has only on very rare occasions been demonstrated in the spinal fluid where we would expect to find it if transmission occurs by the way of these spaces. Another line of evidence is supplied by the fact that the virus is so strictly neurotropic that it probably becomes intimately associated with neurons immediately, in other words, with neurons of the olfactory nerve, which are easily accessible to it.

During recent years much light has been thrown on the pathogenesis of virus diseases in general. A fact which is clearly recognized in viruses is their dependence on tissue cells of one type or another. This is often such a highly specialized dependence that only certain cells may be attacked to the exclusion of all others. From this we must conclude that the requirements for multiplication are met only by very intimate association with the particular cells suited to their propagation, an association such as would result from an actual invasion of the cells which are attacked. That this type of relationship exists is evidenced by the rather distinctive pathology of the virus diseases and by the exacting growth requirements of the viruses when they are cultivated outside of the body. The pathologic effects produced on cells by different viruses range from a rapid degeneration as in poliomyelitis to a stimulation of growth and division as in certain virus induced tumors in animals. In addition to these changes one may observe the presence of characteristic inclusion bodies in the affected cells in many virus diseases. These are generally eosinophilic reaction products which in some infections occur in the cytoplasm, in others in the nucleus. While similar cytologic reaction may be induced by some nonvirus agents and not all virus infections are associated with the formation of inclusions, the presence of such reaction products in a virus disease may, I believe, be regarded as reasonably good evidence that the causal agent is acting from inside the cell.

To what I have just said, I might add that no filter-passing virus has as yet been propagated outside the body in the absence of living tissue cells. While many viruses have now been cultivated outside of the

natural host in cultures of embryonic tissues and in the chorioallantoic membrane of the developing chick, they differ in their capacity to multiply in cells other than those parasitized under natural conditions. The virus of poliomyelitis, for example, has resisted cultivation in various kinds of tissue cultures, and, as Sabin and Olitsky[22] (1936) have recently shown, yields to cultivation in such media only in the presence of nervous tissue from the human embryo. Tissues other than the nervous tissue from the same human embryos failed to provide the conditions necessary for growth, and nervous tissue from the adult monkey also failed to meet the growth requirements of this virus. While we have not had an opportunity to repeat this work with human embryonic tissue, we have spent more than a year in unfruitful efforts to grow the virus in cultures of various other tissues. All of this testifies to the very high selectivity of this virus, a fact which should be remembered in considering the possible routes by which the virus may gain entrance to the body.

Support of the view that the virus probably invades the olfactory nerve directly and reaches the central nervous system through the fibers of this nerve is also to be found in what we know of the pathogenesis of this disease. At one time it was believed that the destruction of the anterior horn cells in the medulla and cord was the indirect result of pressure by inflammatory exudate, a view which was predicated on the presence of an interstitial action. We know now, largely from the work of Hurst and others, that the nerve cell degeneration is a primary phenomenon and that the inflammatory response seen represents a purely secondary reaction. Hurst[23] (1929) came to this conclusion from direct observations of the changes found in different stages of the experimental disease. Later, in collaboration with Fairbrother,[24] he found by sampling different regions of the nervous system during the preparalytic period that the infection spreads along neural pathways. This work was extended by Faber and Gebhardt[25] (1933), who found that by the fourth day following intranasal inoculation the virus becomes established in the olfactory bulbs. By the fifth or sixth day it reaches the hypothalamus, and from here it spreads explosively to the medulla, thalamus, and midbrain, and finally to the cord. Certain portions of the central nervous system, including the frontal and parietal lobes and the cerebellum never contained demonstrable amounts of virus. From this work and a critical review of the literature, Faber[26] (1933) came to the conclusion that throughout its entire course this disease is primarily an infection of the central nervous system, that the virus is transmitted axonally and in intimate association with the neurons from the portal of entry onward.

Recently, Gebhardt and I[27] have extended these studies and not only tested different parts of the central nervous system for the presence of

virus but have titrated the concentration of the virus in different parts of the nervous system as the infection advanced during the preparalytic period. These studies were carried out not so much to satisfy ourselves of the correctness of the earlier mentioned observations, as to check the validity of an hypothesis we have entertained regarding one aspect of the pathogenesis of this disease. This is to the effect that degeneration of susceptible nerve cells does not occur until a certain rather high concentration of virus has been reached—that in the presence of lower concentrations all but very susceptible cells escape damage. We believe that while the virus is transmitted neuronally, injury to the neurons is not necessarily a consequence of an intraneural infection. We believe that nerve cell damage is determined both by the concentration of the virus and the level of resistance of the individual neurons. I cannot discuss this view any further here. I can say, however, that our observations not only lend additional support to the view that the transmission of this virus is primarily axonal, but show also that virus may be present in fairly high concentrations, even in the cord, before any paralysis makes its appearance. It is commonly recognized by experimental workers that in monkeys paralysis of the legs usually precedes paralysis of the arms. This rather frequent observation has suggested to some observers that there must be a fallacy in the theory of axonal transmission, since, if the virus progresses downward from the medulla through the cervical cord, the upper extremities should become involved before the lower. The fact that in man also the legs are commonly involved first has been evoked in favor of the view that the virus enters the central nervous system by the way of autonomic nerves supplying the digestive tract. Our investigations, however, show that the cervical cord may contain a high concentration of virus in advance of its appearance in the lumbar cord. This suggests that the motor nerve cells in the lumbar cord are for some reason more susceptible to this virus than are those in the cervical cord. It seems altogether possible that less usual distributions of paralysis in man may rest on a somewhat greater susceptibility of corresponding groups of nerve cells, rather than that the virus is restricted to the regions showing involvement. At any rate, it may prove helpful in understanding some of these distributions if we bear in mind the possibility that there may be not only an inherent difference in the susceptibility of motor nerve cells in individuals taken as a whole, but that some groups in a given individual may be more susceptible than others.

Also in harmony with an intraneural infection is the presence of inclusion bodies in the nuclei. While not numerous, they have been conclusively demonstrated by Covell[28] (1930), Hurst[29] (1931), and by ourselves (Schultz,[30] 1932) and may be regarded as bearing witness to the location of the virus.

If the evidence I have reviewed concerning the axonal transmission of the virus appeals to you, I should like to put before you this question: How is this virus, which measures only about 10 millimicrons[31] and is among the smallest of the known viruses, actually propagated along the nerve processes? Are autonomously dividing virus particles pushed, carried, or moved along by streaming protoplasm, or, is the virus propagated along the nerve as the result of some catalytic type of action in which one activator particle activates a precursor next to it in series along the axone? Whatever the actual mechanism may be, it is known that the concentration of the virus tends to decrease from above downward after the infection has advanced to the cord[24] and that the concentration in the cord decreases during the days which follow the onset of paralysis. How this inactivation is effected is not known.

It seems clear that once the virus has reached the central nervous system, its propagation is definitely associated with neurons. If we accept this view, it then is not a long step to the concept that the initial infection, under natural as well as under experimental conditions, occurs as a direct invasion of the olfactory neurons in the olfactory mucosa, the only region in the body where nerve cells are exposed to the exterior. We should remember that not only the hairlike endings are exposed at the surface of the olfactory mucosa but also the bulbous enlargements bearing these hairs. This accessibility of neurons to a highly neurotropic virus should explain satisfactorily enough why section of the olfactory tracts prevents the passage of virus to the central nervous system and makes it apparent why the olfactory perineural spaces and the spinal fluid need not be expected to play important roles in carrying it to the central nervous system.

A few investigators do not share this view and believe that in man the olfactory nerve is probably not a frequent portal of entry. On the basis of epidemiologic observations, Kling,[32] of Sweden, in 1929 published the view that the disease may be spread through the medium of water and that the digestive tract may be the most important portal. Experimental observations in collaboration with Levaditi and Lépine[33] (1929) seemed to support this view. However, later work carried out with Levaditi and Hornus[34] (1934) showed quite definitely that it is easier to infect monkeys by the intranasal route than by the alimentary route.

In this country Toomey[35] (1932-1936) has enthusiastically supported the gastrointestinal hypothesis and has offered arguments drawn from both clinical and experimental observations in support of it. I have time only to say that those who do not share his view would point out that the clinical observations to which he has given weight are not necessarily at variance with the more generally accepted view, also, that his experimental procedures have been rather too artificial and drastic to be con-

vincing. It is generally well understood by investigators that any method in which virus is forcibly introduced into the tissues may result in infection. Virus inoculated into the sciatic nerve finds its way to the cord (Hurst,[36] 1930); it does so also following intradermal injection. It should not be surprising then to find that infection follows the injection of virus subserosally into the wall of the gut; that infection results following the introduction of virus into the lumen of the gut under a ballooning pressure; or, that infection follows when virus is introduced there along with toxic substances which help to provide artificial access to nerve terminals in the wall of the gut.

Clark, Roberts, and Preston[37] (1932), Flexner[38] (1936), and especially Lennette and Hudson[38] (1936) have reported observations which demonstrate that when injury to the intestinal mucosa is avoided and something approaching a natural exposure is imitated, it is exceedingly difficult to infect monkeys by this route. While it does not necessarily follow that in man infection by this route would be equally difficult, it is, nevertheless, not yet evident why the intestinal mucosa in man should be any more accessible to this virus than that in the monkey.

Recently Harmon[40] (1937, 1938) has reported that the injection of monkeys with rectal and nasal washings from twenty convalescent patients produced "takes" in only four animals, all resulting from rectal washings. At first glance such an observation seems to afford a strong argument in favor of the intestinal tract as the portal of entry. Let us, however, analyze the possible significance of this observation. In the first place, it seems unlikely that an amount of virus sufficient to be demonstrable in the feces would be ingested with food or water. It is much less likely that virus ingested in any amount multiplies in the gut. We can be certain about this from our knowledge of its exacting growth requirements. How else then can such an amount of virus come to be present in the feces? There is, as I see it, only one satisfactory explanation possible, namely, that it comes to be there as the result of repeatedly swallowing virus-contaminated secretions from the nasopharynx; being highly resistant, the virus is eventually concentrated sufficiently in the gut to be demonstrable. A less likely possibility is that it may be eliminated into the gut from infected autonomic nerves. While it is difficult to demonstrate virus in oral and nasal washings, it has been demonstrated in such washings in patients, in human convalescents, and in infected monkeys (Flexner,[38] 1936; and Kramer, Sobel, Grossman and Hoskwith,[41] 1936). The difficulty of demonstrating virus in such washings probably rests in a large measure on the fact that it is moved downward and outward very rapidly and is not readily detected unless it is present in fairly large amounts. Its low concentration in the nasal washings may indeed mean that higher and more easily

demonstrable concentrations are to be found in tissues and organs which lie below the olfactory area and in a position to receive virus from above. One would, therefore, expect to be able to recover virus from tonsils and adenoids. Indeed, this has been done in convalescents and contacts. Kramer[42] (1935) recovered virus from the tonsils and adenoids of a child who had no known contact with the disease. If it can be demonstrated in the adenoid tissue of the upper respiratory passages, there is then no reason to doubt its reaching the digestive tract from the same general source. Until recently, however, little success has attended attempts to recover virus from the stools of human beings or of monkeys dying of the disease, even with the aid of methods for concentrating any virus that might happen to be present (Clark, Roberts and Preston, 1932[37]; and Flexner, 1936[38]).

Important arguments against the theory that the olfactory nerve in man is the common pathway for this virus are the observations made by Landon and Smith[43] (1934) on some fifty-six olfactory bulbs from fatal human cases. They found surprisingly little pathologic change in most of the bulbs which they examined. While edema and congestion were rather frequently observed, fewer than one-fourth showed cellular infiltrations. They conclude that either the inflammatory reaction is short lived, or the virus passes along these structures without leaving traces. A third possibility seemed more logical, namely, that in human beings the olfactory bulb is not necessarily a frequent pathway and that nerve roots elsewhere may be of equal importance as portals of entry, possibly indirectly by the way of the blood stream to their ganglia. Harmon and Levine[40] (1938) have reported that only two of nine fatal cases disclosed lesions in the olfactory bulbs. Such negative observations as these are, of course, of great important, especially in the light of the recent observations of Sabin and Olitsky[44] (1937), who have found that the olfactory bulbs of intranasally infected monkeys show definite lesions, which are absent when the invasion of the nervous system has been by other pathways. They found, however, that the type and extent of the lesions varied considerably and that one of the olfactory bulbs frequently showed more extensive lesions than the other. In almost a third of the animals receiving instillation of virus in both nares, only unilateral involvement of the bulbs was observed. Such observations suggest that in man minor lesions may be altogether missed unless both bulbs are carefully examined by the serial section method. After all, should one necessarily expect to always find lesions in the olfactory bulbs in man? I, personally, do not feel certain that the virus always leaves an easily recognizable trail to mark the route it has taken. In any case a more extensive study of the olfactory bulbs from fatal cases in man is certainly needed now to help clear up this important question. Sabin and Olitsky, at the Rockefeller Institute, are at present

engaged in such a study and will, I know, greatly appreciate the cooperation of pathologists who send them such material for study.

Before I leave the question of the portal of entry, I should refer briefly to recent observations (Trask and Paul,[45] 1936, 1938; and Howitt,[46] 1937) which indicate that freshly isolated, so-called human strains exhibit a greater capacity to infect monkeys by intradermal inoculation than do monkey passage strains, the practical inference being that natural infection in man may possibly result from cutaneous contact with virus. What the actual practical significance of these observations really may be is yet too early to say. This much, however, may be said. All the facts to date seem to indicate clearly that the virus of this disease is highly neurotropic and is capable of multiplying only in nervous tissue. Since this is true, it would be indeed surprising to find that it can spontaneously establish itself in the nervous tissue of a new host by penetrating a barrier so unfavorable as squamous epithelium. This would prove especially surprising in view of the fact that even an intact mucous membrane affords a considerable barrier for this virus. I have already mentioned that in monkeys infection by the gastrointestinal tract is difficult if we take care not to traumatize the mucosa. I have also mentioned that after cutting the olfactory tracts, one may instill virus freely and repeatedly into the nasal passages without inducing infection. It appears then that infection through intact mucous surfaces does not occur. It would seem, therefore, that to have infection through the skin, one would have to presuppose an abrasion or injury sufficient to allow a skin containing virus to come in contact with cutaneous nerves. That such a combination of circumstances may play an important part in the epidemiology of this disease seems unlikely from the information we have at the present time.

I have dwelt at some length on the portal of entry because any prediction as to the value of chemoprophylaxis in the control of this disease must depend in the first place on how valid the evidence is that the olfactory nerve is the usual portal of entry. If it is not the usual portal in man, then my story ends here. If it is the usual portal, then I can go on and say that the future of chemoprophylaxis as a practical measure depends on the eventual answers to at least three important questions: (1) Are the results which have been obtained in monkeys transferable to man? (2) Are the practical difficulties of applying such a prophylactic measure in man sufficiently surmountable to make it a reasonably attractive public health measure? And (3) are there any serious contraindications to the general use of such a prophylactic measure?

ARE THE RESULTS OBTAINED IN MONKEYS TRANSFERABLE TO MAN?

Whether or not the results which have been obtained in monkeys are in any measure transferable to man is still too early to say. Observations with the picric acid-alum spray in Alabama in 1936 were incon-

elusive, but, as Armstrong[47] has pointed out in his analysis of this field test, the results in this test could not have been anything more than inconclusive in the absence of a dependable method of applying the prophylactic treatments. We now know that solutions cannot be applied to the olfactory area with an ordinary atomizer. It follows as a corollary that there can be no evaluation of this type of prophylaxis in the absence of a method which can be depended upon to bring the solution in contact with all of the olfactory surface. I want to emphasize this, for I have heard the Alabama experience mentioned as evidence that chemoprophylaxis has nothing to offer. I grant that eventually the application of chemical solutions may be proved worthless in preventing the disease in man, but we should be sure to view such an experience in the proper light—as a failure in the technique of its application and not necessarily as evidence against the protective value of the agent used.

Unfortunately, the Alabama field test is not the only field test which has failed to contribute an answer to our first question. From another report it appears that a second field test, carried out during the past summer in Toronto, in which zinc sulfate solution was used, also failed to yield information on this point. The report to which I refer appeared in the November (1937) issue of the *Canadian Public Health Journal* under the authorship of Tisdall and others.[48] It presents the results obtained on a group of about 5,000 children treated with zinc sulfate solution. These treatments were carried out according to a technique recommended by Peet, Echols, and Richter[49] (1937), which I shall describe later. Here, too, the results were such as to suggest, on superficial examination of the data, that the measure is not of value in man, for in a group of 4,713 children sprayed twice at intervals of ten to twelve days there were 11 cases of poliomyelitis, with only 18 cases in a control group of 6,300. In the period from seven days after the first spraying to thirty days after the second spraying the attack rate was 2.1 in the sprayed group and 2.9 in the control group. Statistically, there was no significant difference between the two groups. In writing their conclusions, they stated that their study furnishes no evidence of the protective value of the "spray." While this statement is basically correct, it is a little misleading without some qualification to indicate that the success of the measure might have depended somewhat on how thoroughly the solution was applied to the portal of entry. The following statement in the body of the report helps to convey the impression that this particular field test was in a sense crucial. It reads: "In the opinion, however, of the attending otolaryngologists, the olfactory area was satisfactorily sprayed in the majority of children." Since this is an important statement let us examine the data presented for evidence that this was true. Probably the only dependable criterion at present

available of complete coverage of the olfactory area is the development of anosmia. Their figures show that of a total of 5,233 children sprayed, less than 20 per cent were tested for the presence of anosmia and that of the total number tested a grand average of only 14 per cent showed impairment of the sense of smell. The degree of the impairment and its duration are not discussed. At any rate, we must conclude from the figures they themselves have given us that in about 85 per cent of those sprayed the solution was not applied thoroughly enough to cover all of the olfactory area. Naturally, any failure to cover this area tends to invalidate conclusions drawn as to the prophylactic value of the solution used. The only conclusion which seems justifiable from the results of this field test is that the method of applying the solution failed.

But while this field test also failed to give us information as to the effectiveness of chemical prophylaxis in man, some information has been gathered which should prove helpful in conducting future field tests. Foremost is the probable importance of using the presence of anosmia as a criterion of adequate treatment. There can be no assurance that the olfactory area has been completely covered unless anosmia is produced in all individuals treated. Furthermore, functional tests repeatedly applied to determine the continued presence of anosmia should be, I believe, the basis for deciding the interval of time which may elapse between treatments, rather than results obtained in monkeys. We now know that anosmia invariably follows a thorough application of zinc sulfate solution, and, since this is the case, there can be no better guide as to when another treatment is due. The method employed for testing the anosmia should be entirely dependable, one in which the results are not influenced by natural anatomic conditions in the nose. Such a method, I understand, is that devised by Esbach. I can appreciate what all this testing would mean from the standpoint of time and skill, but I see no easier road to the information we now need. It seems certain that a sufficient number of functional tests will have to be carried out in the beginning to determine whether the method employed for applying the solution can be depended on to cover the olfactory area completely. As to the interval of the treatments, experience will have to be our guide if the duration of the anosmia is to serve as a criterion.

ARE THE PRACTICAL DIFFICULTIES OF APPLYING SUCH A PROPHYLACTIC MEASURE IN MAN SUFFICIENTLY SURMOUNTABLE TO MAKE IT A REASONABLY ATTRACTIVE PUBLIC HEALTH MEASURE?

Unfortunately, the olfactory area in man is rather inaccessible. Because the middle turbinate tends to encroach on the septum, the chances of adequately covering this area with an ordinary atomizer are small. To surmount this obstacle Peet, Echols, and Richter[49] (1937) suggested the use of a special atomizer tip, which can be introduced along the sep-

tum past the middle turbinate. This special tip overcomes some of the difficulties, but to use it requires the service of a nose and throat specialist. It is hazardous in the hands of unskilled operators and cannot be applied to young children and others who do not cooperate fully. The fact that in the Toronto outbreak of poliomyelitis the use of this method resulted in producing an anosmia in less than 15 per cent of those treated suggests that it is not trustworthy, even in the hands of nose and throat specialists.

Measures are often discovered when a need becomes urgent. The need for a simple and effective method for covering the olfactory area has not existed before. To most of us this area is new territory. Therefore, it is not surprising that a simple way to inundate this surface with a medicinal solution had to be discovered.

During recent months it has become evident that this can be accomplished without the aid of an atomizer and with little or no instrumentation. It has been established that when the head is completely inverted, a fluid properly introduced into the nares will flow freely into and fill the superior meatal space.

Before I enlarge on this observation, I want to refer briefly to a method introduced by Pentecost[50] (1937) during the recent epidemic in Toronto. Anticipating that he might be called upon to apply zinc sulfate, Pentecost began experiments in July to ascertain the best method for applying the solution. He settled on a technique which consisted of introducing the solution with the aid of a flexible olive-tipped ureteral catheter. This he inserted between the nasal septum and the middle turbinate; then, with a Luer syringe attached to the free end, 0.5 c.c. of the solution was forced through the catheter, the patient being recumbent with the head in the Proetz position ("head inverted so that the chin and external auditory meatuses are in the same vertical plane"). This procedure seemed the easiest to carry out, the least hazardous, and the least discomforting to the patient. Especially noteworthy is the fact that by this method immediate anosmia was produced in 100 per cent of those treated. Approximately 100 children, 8 years of age and older, were treated in this way with no serious effects. The method, unfortunately, was developed too late to receive more extensive application in this outbreak. There were no cases of poliomyelitis among those treated by the method, but, of course, the group was too small for this to be of any significance.

Early during the past summer Shahinian, Bacher, McNaught and Newell[51] at Stanford undertook studies to determine the best way of applying solutions to the olfactory area. Soon after they began this work they showed me a method which was similar to that described a short time later by Pentecost. However, they abandoned this method when they discovered that correct posture alone suffices to overcome

much of the difficulty. The Proetz position, a position commonly used in filling the sphenoidal sinuses with solution, was recognized as not an optimum position for obtaining good coverage of the olfactory area. From radiologic and other observations it became evident that when the head is completely inverted, that is, when the line between the infra-orbital ridge and the external auditory meatus is in the horizontal plane, limited quantities of the fluid, if introduced slowly into the olfactory sulcus at the limen nasi, will flow along the nasal groove and fill the inverted common nasal meatus in a highly selective manner and to a height usually sufficient to immerse most of the estimated olfactory area. This method was found fully as efficient as direct placement of fluid by means of a delicate ureteral catheter introduced between the middle turbinate and septum.

To apply the solution by this procedure, the patient is put on a table with the head in the fully inverted position. A maximum of 0.5 c.c. of fluid is then introduced slowly and steadily, drop by drop, with a medicine dropper into each nasal space. After the required amount has been introduced, the patient is kept in the inverted position for one minute. He is then turned over to the prone position and instructed to lift his head and sniff outwardly to help discharge any excess fluid. Previous shrinkage of the mucous membranes is believed unnecessary and probably undesirable.

Information from other groups of nose and throat specialists investigating this question indicates that this purely postural method is finding favor. It is much more easily carried out than the spray method and can be applied by any physician or public health worker after a little instruction.

ARE THERE ANY CONTRAINDICATIONS TO THE GENERAL USE OF ZINC SULFATE AS A PROPHYLACTIC MEASURE?

This question deserves careful consideration. In addition to temporary discomfort, such as local irritation and headache lasting for several hours, which is more severe in adults than in children, there is possibly some risk of inducing a lasting anosmia. I have emphasized the importance of applying the treatments thoroughly enough to induce anosmia, but no one wants such an effect to be permanent. While the information I have obtained to date from various sources indicates that the anosmia induced by zinc sulfate solution in the vast majority of cases disappears in less than two weeks, I have also been informed of cases in whom the sense of smell did not return until after periods of two to four months. While I have no knowledge at this time of permanent anosmia having been produced in any one, nevertheless, I feel that there is this risk, one which may be greater if the treatments are carried out with temporary anosmia as an objective. Dr. Pentecost has recently informed me that all of his group have now regained the sense of smell,

"although in a few it is still not 100 per cent." So far as my information goes, all of the cases of more lasting anosmias have been in adults, in whom the immediate local reaction following treatment is likely to be much more severe than in children. This posttreatment reaction is associated with a more or less severe headache, which generally begins about twenty minutes following the application of the solutions and lasts from three to six hours. The headache is usually frontal, localized between the eyes and referred to the occiput. I am told that it ends suddenly, as though a hot iron had suddenly been removed. This difference between adults and children, both in the severity of the immediate reaction and in the duration of the anosmia may possibly be explained on an anatomic basis. In adults the superior meatus is narrower than in children;[51] it may indeed be narrow and deep enough to hold considerable solution by capillary action. This would naturally result in a solution being held in contact with the olfactory mucosa for a longer period of time than would be likely in children, who have a wider superior meatus. Such longer contact would of course intensify and prolong the immediate discomfort and no doubt add to the local injury, whatever the character of this injury may be. One may well ask, is there a relationship between the degree of this immediate reaction and the duration of the anosmia? Is an immediate edema as well as more intense drug action responsible for the pain? Is the more lasting anosmia in adults due in part, at least, to a persisting inflammatory reaction, or, does it rest wholly on a more profound injury to the olfactory apparatus, the result of prolonged and uncontrolled drug action? If the latter is the case, how may we account for the return of function months after treatment? I wish that I could answer these questions. The answers would, no doubt, be more apparent if we knew more about the way zinc sulfate acts in producing protection in monkeys. I recall that during the early part of our studies, I experienced at one time considerable uneasiness when it occurred to me that the protection we had observed might have resulted from an edema of the olfactory mucosa, closing off mechanically the very narrow olfactory cleft. However, careful dissections of the area in untreated and recently treated monkeys ruled out this possibility. It was ruled out also by the fact that the protection in monkeys often lasts for several months.

I would not have you believe that we are unmindful of the possibility that the protection observed may be the result of an actual destruction of the olfactory receptors. In this case susceptibility or the sense of smell would not be expected to return unless structural regeneration can and does take place. This brings up the question, to what extent can the olfactory nerve regenerate? We, of course, all know that ordinary nerve cells are not restored and that only the dendrites and axones of otherwise normal neurons can be regenerated, but so far as I know there is no information available bearing on the regenerative

powers of the olfactory nerve. To me it does not seem entirely improbable that these rather primitive receptors, whose cell bodies are no doubt exposed to naturally induced injuries, may possess powers of regeneration beyond those we see in ordinary nerve cells. As I have already pointed out, there are certain reasons for keeping open minded on this question; among these are the restoration of susceptibility in monkeys and the restoration of the sense of smell in man after a prolonged anosmia.

During recent months we have been engaged in studies designed to determine how the resistant state in monkeys is produced, especially with a view to determining whether the protection is associated with recognizable anatomic changes in the olfactory cells or their peripheral processes. This investigation has proved more difficult than we anticipated. An important difficulty lies in the lack of altogether practical staining methods for demonstrating olfactory cells and their processes. In describing the structure of the normal olfactory mucosa, I spoke with some assurance on the differences between three types of cells found in the membrane. However, when one is confronted with the immediate problem of identifying olfactory cells with certainty, he begins to appreciate some of the difficulty which attends such a study. With regard to the more obvious histologic changes, we can say that varying grades of exudative inflammation may be present in the olfactory mucosa even a week or more after treatment, but this is frequently no more than one may observe in untreated monkeys. One may also see some desquamation of the olfactory epithelium, but this also is sometimes observed in sections from normal monkeys. There may be some disorder in the arrangement of the epithelial cells. This, too, has been observed in the olfactory mucosae of some untreated monkeys.

Recently we have examined membranes removed one to five days after treatment. These examinations were prompted by evidences of epithelial regeneration in several membranes which were removed two days after treatment, also, by the fact that the membranes from some of the monkeys treated a week or so previously presented certain signs of having been repaired. What is important is that several membranes removed a day after treatment with 1 per cent zinc sulfate have presented a marked exudative inflammation associated with some desquamation and necrosis of epithelial cells. This inflammation, however, seems to subside rapidly and to be followed very promptly by regeneration of the epithelium. To what extent the olfactory nerve cells themselves figure in this regeneration, if at all, is now being investigated. At present we can only say that if the protection described is wholly the result of a destruction of the peripheral processes of the olfactory cells, or of the cell bodies themselves, it must then follow that there is regeneration of these processes, possibly even of olfactory cells. This only would explain

why practically all monkeys become susceptible again to intranasal instillation of virus several months after the treatments. A regeneration of the peripheral processes only would not be novel, but evidence that destroyed neurons are replaced in some way would indeed be new.

I wish to repeat, however, what I said earlier, that it is quite possible that the protection may result, in part at least, from a more or less lasting chemical union of the zinc ion with the dendrite of the olfactory cell, altering its permeability but not necessarily associated with visible anatomic change, or the dendrite alone may be destroyed and subsequently regenerated.

In closing, I should like to make a few more general remarks regarding this type of prophylaxis. Should further field tests show that chemical agents can be used effectively in preventing this disease in man, and should there prove to be no serious contraindications to the widespread use of such a measure, regarding which we may well be uncertain, this would still leave us with a measure which would be far from ideal. It would not be ideal for the reason that such protection as may be afforded would be at best of short duration, thus making it necessary to repeat the treatments several times during the "polio" season. Furthermore, it would not be practical to use it widely enough to protect against the more sporadic occurrence of the disease. Its usefulness would be limited to checking an incipient epidemic, after enough "sentries" give the signal that an epidemic is approaching. An ideal prophylactic measure would be one that would be sufficiently effective to help stamp out the disease entirely. Because of the relatively short duration of the protection and the unlikelihood that a chemical measure ever will be applied to a large part of the population, it is not likely to afford an effective means for the eventual conquest of this disease. But while all this is true, such a measure seems to possess certain virtues not likely to be found in methods which may leave a more lasting immunity. A chemical solution is simple to prepare and inexpensive. It carries nothing which may induce infection and probably will prove simple enough to apply. I am aware there are many who cherish the hope that a method will be found by which a permanent resistance to this disease may be artificially induced, possibly by the application of a specific antigen to the olfactory area. While I would be unwilling to say that there is no prospect of such a solution of the problem, such a measure would have to be not only proof against accidental infections, but financially within reach of the public purse to have wide application. Any measure which requires material from infected monkeys is likely to prove prohibitive from the cost angle alone. This cost, of course, would prove considerably less if we had a simple test to identify those in need of artificial help, but from the results of extensive studies in our laboratory and elsewhere I can say that such a test is not in prospect.

Because of these facts, it is my opinion that the possibilities of chemical prophylaxis should be explored further, for at the present moment such a measure seems to offer the only promise of a practical solution. Investigations should be continued to elicit the most effective, the least irritating, and least harmful agent for trial in man; there should be an agreement on what constitutes a thorough application and how frequently a solution should be applied to insure a continued effect. Above all, we need a satisfactory field test to tell us whether this type of prophylaxis, so effective in monkeys, is in any measure applicable to man.

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PERSISTENT ANOSMIA FOLLOWING ZINC SULFATE NASAL SPRAYING

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DURING the outbreak of poliomyelitis which occurred in Toronto during the months of August, September, and October, 1937, a study[1] was conducted to furnish information concerning the possible prophylactic value of the zinc sulfate nasal spray, the use of which was suggested by the findings of Schultz and Gebhardt,[2] and Peet, Echols, and Richter.[3] Observations were made on a group of 4,713 children, aged 3 to 10 years, who received two sprayings with an interval between the sprayings of ten to twelve days, and 520 additional children who received only one spraying. The spraying was conducted in special clinics by otolaryngologists. Schultz and Gebhardt, and Peet and his collaborators expressed their belief that the satisfactory covering of the olfactory area was indicated by the loss of the sense of smell. From the observations made in the Toronto study, it would appear that not more than 25 per cent of the children sprayed developed anosmia (temporary). Inquiries have indicated that very few, if any, of the children who were sprayed in the special clinics reported subsequently to the various hospital clinics complaining of persisting anosmia. It is to be remembered that this age group consisted of children of from 3 to 10 years of age.

Through the cooperation of the otolaryngologists of the various city hospitals, reports were supplied concerning the persons sprayed by them in their private practice. Data were kindly furnished regarding age and the number of sprayings. Information was also supplied concerning the presence of anosmia at the end of two months, with or without disturbance of the sense of taste, and similar information at the end of six months. Reports were received from thirty-two otolaryngologists. Statements were not made in their reports concerning the method of determining the loss of the sense of smell or the disturbance of the sense of taste. The number recorded having anosmia with or without disturbance of the sense of taste at the end of two months was thirty-six, and the number at the end of six months was fifty-two, indicating that a number of patients did not consult their otolaryngologist until several months had elapsed. These data, arranged in age groups, are presented in Table I; in Table II, data are presented, arranged according to the number of sprayings.

From the Hospital for Sick Children and the School of Hygiene and Connaught Laboratories, University of Toronto.

TABLE I

PATIENTS REPORTING DISTURBANCE OF SENSE OF SMELL WITH OR WITHOUT DISTURBANCE OF SENSE OF TASTE

(Toronto, 1937)

AGE (YR.)	AFTER 2 MONTHS				AFTER 6 MONTHS			
	SMELL ONLY	TASTE ONLY	SMELL AND TASTE	TOTAL	SMELL ONLY	TASTE ONLY	SMELL AND TASTE	TOTAL
Less than 10	2	3	–	5	–	–	1	1
10 to 14	4	–	4	8	1	4	5	10
15 to 19	7	4	5	16	5	3	13	21
20 to 24	2	2	–	4	1	1	13	15
More than 25	–	–	3	3	–	–	5	5
Total	15	9	12	36	7	8	37	52

TABLE II

DISTURBANCE OF SMELL AND TASTE IN RELATION TO THE NUMBER OF SPRAYINGS

(Toronto, 1937)

NO. OF SPRAYS	AFTER 2 MONTHS				AFTER 6 MONTHS			
	SMELL ONLY	TASTE ONLY	SMELL AND TASTE	TOTAL	SMELL ONLY	TASTE ONLY	SMELL AND TASTE	TOTAL
1	–	1	3	4	1	–	10	11
2	11	8	9	28	6	7	26	39
3	4	–	–	4	–	1	1	2
Total	15	9	12	36	7	8	37	52

Although data were not available regarding the total number of persons sprayed by the various otolaryngologists, the total number probably did not exceed 5,000. That this is not too conservative an estimate is indicated by the fact that records of only 741 children receiving two sprayings in private practice were received from the otolaryngologists of the city for inclusion in the report of the original study. The findings as presented in Table I indicate that the complaint of persistent anosmia occurred more frequently in the older age groups. Although it is not possible to state the methods of testing the sense of smell used by the various otolaryngologists, there can be little doubt that these patients at the end of six months had definite complaints of disturbance of the sense of smell and, in many instances, of taste. It will be noted from Table I that only five children less than 10 years of age were reported by the group of otolaryngologists, in their private practice, as having anosmia at the end of two months and only one at the end of six months. These findings are in accord with the opinion of the attending otolaryngologists that few, if any, of the children who received the nasal spraying in the special clinics subsequently suffered from a continuing disturbance of the sense of smell. Persisting disturbance of taste and smell was noted in eleven cases (Table II), in which the patients received only one spraying, and in thirty-nine who received two sprayings. The clinical reports relating to the fifty-two patients, who at the end of six months had disturbances of the sense

of smell and taste, include patients with marked loss of the sense of smell as well as others in whom the sense of smell is returning. Some complained of unpleasant odors and others of a distorted sense of smell. Disturbances of taste were frequently associated with disturbances of smell (Table I).

DISCUSSION

Schultz and Gebhardt based their belief that the application of 1 per cent zinc sulfate with 0.5 per cent pontocaine, in the small amounts required to cover the olfactory area, would not produce any undesirable or harmful effects on the finding that no noteworthy gross or microscopic changes were found in the nasal mucous membranes of monkeys treated repeatedly with zinc sulfate, other than a mild grade of inflammation. Peet and his collaborators recorded anosmia following the application of the spray in a group of medical students but found that the sense of smell returned within one or two weeks. Dr. Peet[4] reported that all children sprayed by him and by his associates in Michigan last summer had been re-examined, and in every one the sense of smell had returned. In some adults, however, the sense of smell did not return to normal for three months or even longer.

The persisting disturbance of sense of smell and taste in certain individuals, after a period of six months, is difficult to explain on the basis of a persisting inflammation of the olfactory mucous membrane, causing a mechanical blocking of the olfactory area. A study of the changes in the olfactory mucous membrane following the instillation of zinc sulfate in rats,[5] and similar observations made in ferrets[6] suggest that the effect of a one per cent solution of zinc sulfate on the mucous membrane of human beings should be c refully studied to determine if the persisting disturbance of smell and taste may be due to injury to the olfactory area.

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ACUTE ANTERIOR POLIOMYELITIS FOLLOWING TONSILLECTOMY AND ADENOIDECTOMY

With Special Reference to the Bulbar Form

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THE portal of entry of the virus of poliomyelitis into the central nervous system has always received a great deal of attention and even today warrants further clinical and experimental study. The fact that the bulbar form of acute anterior poliomyelitis has been reported[1, 2] following recent tonsillectomy and adenoidectomy has suggested that this procedure might, in some manner, influence the entrance of the virus. A study of 418 consecutive patients with acute poliomyelitis admitted to the medical wards of the Infants' and the Children's Hospitals of Boston adds further evidence as to this possibility and strongly suggests that in those instances in which the operation is of an elective nature, it may be advisable to postpone it during that period when poliomyelitis is prevalent. The following information is offered in support of this statement.

Table I

Total Number of Admissions of Patients With Acute Poliomyelitis

Number of cases of spinal poliomyelitis	287
Number of cases of bulbar poliomyelitis	131
Total number of admissions	418

The large percentage of bulbar poliomyelitis cases included in the total number of admissions in Table I is striking. This is probably explained by the fact that this form of the disease causes deeper concern than the spinal form, with the result that the patient suffering from bulbar poliomyelitis is more frequently referred to the hospital.

CASES OF ACUTE ANTERIOR POLIOMYELITIS

Record No. 154106.—J. R., female, 4¼ years of age, had a tonsillectomy and adenoidectomy on Oct. 14, 1931, and on Oct. 24, 1931, complained of headache and malaise. Two days later she developed a stiff back, resisted anterior flexion of her head, and complained of headache. On October 28 she was admitted to the hospital with temperature 101° F., pulse rate 120 per minute, and respiration rate 28 per minute. The physical examination and the examination of the cerebrospinal fluid were sufficient to warrant a diagnosis of acute anterior poliomyelitis. A few days after her entry the patient developed weakness of her abdominal muscles.

Record No. 182418.—J. I., male, 5 years and 11 months old, had a tonsillectomy and adenoidectomy on Aug. 13, 1934, and on Sept. 7, 1934, he complained of head-

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ache, malaise, abdominal pain, and developed a temperature of 102° F. During the following thirty-six hours these symptoms persisted, but for the next twelve hours he felt well so was allowed out of bed. When he began to walk he complained of weakness in his legs. On admission to the hospital his temperature was 102.6° F., pulse rate, 115 per minute, and respiration rate, 25 per minute. Examination revealed definite signs of meningeal irritation and weakness of the extensor muscles of the lower extremities. The changes in the cerebrospinal fluid were consistent with those noted in acute poliomyelitis.

Record No. 214299.—B. P., female, 4½ years of age, had a tonsillectomy and adenoidectomy performed on July 1, 1937. On July 26, 1937, she complained of headache and pains in her muscles. On July 29 these hyperesthesias of her muscles became more pronounced, her neck resisted anterior flexion, and her back was stiff. On August 2 she was admitted to the hospital with a temperature of 98.6° F., pulse 120 per minute, and respiration 28 per minute; there was weakness of the right shoulder girdle. Examination of the cerebrospinal fluid showed clinic and cytologic changes consistent with a diagnosis of acute anterior poliomyelitis.

Record No. 214691.—G. J., male, 5 years and 9 months of age, had a tonsillectomy and adenoidectomy performed on July 22, 1937. On Aug. 18, 1937, he developed a temperature, headache, and became irritable. At the time of examination, August 22, his temperature was 101.4° F., pulse 130 per minute, and respiration 40 per minute. The neck resisted anterior flexion, the back was stiff, and there was weakness of the right lower extremity. Examination of the cerebrospinal fluid presented changes consistent with acute anterior poliomyelitis.

Record No. 138479.—H. P., male, 3 years and 10 months of age, had a tonsillectomy and adenoidectomy on July 27, 1930. On August 26 he became restless, complained of headache and abdominal pain. The following day the same symptoms were present and there was temperature, resistance to anterior flexion of the neck, and stiffness of the back. On admission the temperature was 99.8° F., pulse 140 per minute, and respiration 40 per minute. The physical examination as well as the examination of the cerebrospinal fluid supported a diagnosis of acute anterior poliomyelitis.

Record No. 142785.—C. K., male, 9 years of age, had a tonsillectomy and adenoidectomy on Aug. 29, 1930, and on Oct. 1, 1930, complained of headache, abdominal pain, and nausea. On the following day the patient vomited, continued to complain of headache, and developed a temperature, stiff neck, and stiff back. On admission his temperature was 100.4° F., pulse 90 per minute, and respiration 25 per minute. The physical examination and the examination of the cerebrospinal fluid warranted a diagnosis of acute anterior poliomyelitis.

PATIENTS WITH BULBAR POLIOMYELITIS

Record No. 108099.—J. S., female, 7⅓ years of age, had her tonsils and adenoids removed on Aug. 11, 1927, and on Aug. 21, 1927, she became nauseated, complained of a headache, and regurgitated fluid through her nose. At the time of admission to the hospital on August 22 her temperature was 100.4° F., pulse 110 per minute, and respiration 20 per minute. Physical examination and examination of the cerebrospinal fluid supported the diagnosis of acute anterior poliomyelitis with pharyngeal paralysis.

Record No. 62593.—D. V., male, 4 years and 11 months of age, had a tonsillectomy and adenoidectomy performed on Aug. 5, 1927. On August 15 he complained of malaise, headache, and vomited. On August 18 he developed a nasal voice, became unable to swallow, and regurgitated fluids through his nose. At the time of admission to the hospital his temperature was 100.4° F., pulse 120 per minute, and

respiration 24 per minute. The physical examination and the examination of the cerebrospinal fluid confirmed the diagnosis of acute anterior poliomyelitis with pharyngeal paralysis.

RECORD No. 108514.—M. D., female, 8 years of age, had her tonsils and adenoids removed on Aug. 14, 1927, and on Aug. 24, 1927, she became drowsy, irritable, and complained of a headache. On August 28 her speech became indistinct and some difficulty was encountered on swallowing. At the time of her admission, August 30, her temperature was 104° F., pulse 120 per minute, and respiration 30 per minute. Physical examination and examination of the cerebrospinal fluid confirmed the diagnosis of acute anterior poliomyelitis with pharyngeal paralysis.

RECORD No. 162714.—W. E., male, 6 years of age, had a tonsillectomy and adenoidectomy performed on July 22, 1933, and on Aug. 6, 1933, complained of headache and malaise; he refused food and developed a temperature. On August 8 he complained of stiff neck and back, and on August 9 he became unable to swallow fluids. At the time of admission his temperature was 101° F., pulse 130 per minute, and respiration 30 per minute. Physical examination and examination of the cerebrospinal fluid warranted a diagnosis of acute anterior poliomyelitis with right facial paralysis and partial paralysis of both shoulders and left hip.

RECORD No. 162675.—M. McG., female, 4 years and 2 months of age, had a tonsillectomy and adenoidectomy on Aug. 16, 1932, and on Aug. 28, 1932, she developed a temperature and vomited. Twenty-four hours later she complained of a stiff neck and back. On August 30 her voice assumed a nasal tone and she began to regurgitate fluids through her nose. Physical examination and examination of the cerebrospinal fluid established a diagnosis of acute anterior poliomyelitis with pharyngeal paralysis.

RECORD No. 153356.—A. T., female, 6¾ years of age, had her tonsils and adenoids removed on Sept. 11, 1931. On Sept. 21, 1931, the school teacher observed that the child had a nasal voice and seemed to swallow with difficulty. The child was sent home from school and on the following day admitted to a hospital where the diagnosis of acute anterior poliomyelitis with pharyngeal paralysis was made. On September 26 she was transferred to the Children's Hospital where the same diagnosis was made, as the physical examination and examination of the cerebrospinal fluid were consistent with this infection.

RECORD No. 195745.—E. B., male, 9 years of age, had a tonsillectomy and adenoidectomy performed on Sept. 1, 1935. On Sept. 14, 1935, he developed a temperature, vomited, and complained of difficulty in swallowing. He was admitted to the hospital on September 15, at which time his temperature was 102.4° F., pulse 106 per minute, and respiration 24 per minute. Physical examination and examination of the cerebrospinal fluid established the diagnosis of acute anterior poliomyelitis with pharyngeal paralysis.

RECORD No. 191189.—J. D., male, 4¾ years of age had his tonsils and adenoids removed on July 31, 1935, and on August 14 complained of malaise, headache, and developed a nasal voice. He was admitted to the hospital on August 17, at which time his temperature was 101.6° F., pulse 152 per minute, and respiration 32 per minute. Physical examination as well as examination of the cerebrospinal fluid established the diagnosis of acute poliomyelitis with pharyngeal paralysis.

RECORD No. 153131.—M. T., female, 6 years of age, had a tonsillectomy and adenoidectomy performed on Sept. 2, 1931. On Sept. 16, 1931, she became listless and complained of being tired. The following day she became unable to swallow fluids. At the time of admission her temperature was 102.4° F., pulse 140 per minute,

and respiration 24 per minute. Physical examination as well as the examination of the cerebrospinal fluid confirmed the diagnosis of acute anterior poliomyelitis with pharyngeal paralysis.

RECORD NO. 142337.—G. B., female, 6 years and 2 months of age, had her tonsils and adenoids removed on Sept. 4, 1930. On Sept. 18, 1930, she complained of headache and developed a temperature of 101.6° F. Forty-eight hours later she began to regurgitate fluids, and her voice became nasal in character. On admission, her temperature was 102.4° F., pulse 90 per minute, and respiration 30 per minute. Physical examination and examination of the cerebrospinal fluid confirmed the diagnosis of acute anterior poliomyelitis with pharyngeal paralysis.

RECORD NO. 124487.—T. K., male, 2¾ years of age, had his tonsils and adenoids removed on Aug. 3, 1931. On Aug. 17, 1931, he became irritable and fussy, developed a nasal voice, and began to regurgitate fluids. At the time of admission his temperature was 103° F., pulse 130 per minute, and respiration 30 per minute. Physical examination and examination of the cerebrospinal fluid confirmed the diagnosis of acute anterior poliomyelitis with pharyngeal paralysis.

RECORD NO. 172937.—M. N., female, 6 years and 2 months of age, had her tonsils and adenoids removed on Aug. 7, 1933, and on Aug. 22, 1933, became sick with temperature, nausea, malaise, and headache. The following day, August 23, her neck became stiff, and her voice developed a nasal quality. She was admitted to the hospital on August 24 with temperature 99.8° F., pulse 92 per minute, and respiration 24 per minute. Physical examination disclosed paralysis of the pharynx and stiff neck. The changes in the cerebrospinal fluid were consistent with those noted in acute anterior poliomyelitis.

RECORD NO. 188272.—N. M., female, 5 years and 5 months of age, had a tonsillectomy and adenoidectomy performed on Aug. 28, 1935. On September 13, after a day or two of not feeling very well, the child developed a nasal voice and began to regurgitate fluids through her nose. She was admitted to the hospital on September 15, at which time her temperature was 102.8° F., pulse 128 per minute, and respiration 28 per minute. The physical examination and the cytochemical changes within the cerebrospinal fluid confirmed the diagnosis of acute anterior poliomyelitis with pharyngeal involvement.

RECORD NO. 109687.—P. L., male, 6½ years of age, had his tonsils and adenoids removed on Sept. 27, 1927. On Oct. 13, 1927, he complained of headache, muscle pains, and fever. At the time of admission, Oct. 17, 1927, his temperature was 99.8° F., pulse 110 per minute, and respiration 20 per minute. Physical examination and examination of the cerebrospinal fluid supported a diagnosis of acute anterior poliomyelitis with right facial paralysis.

RECORD NO. 153511.—R. P., male, 5 years and 1 month of age, had a tonsillectomy and adenoidectomy on Aug. 21, 1935, and on Sept. 8, 1935, he developed a temperature, headache, stiff neck, and began to talk with a nasal voice. On September 10 he was admitted to the hospital, at which time his temperature was 102.2° F., pulse 120 per minute, and respiration 24 per minute. Physical examination and the examination of the cerebrospinal fluid warranted a diagnosis of acute anterior poliomyelitis with pharyngeal paralysis.

RECORD NO. 152204.—E. B., male, 9 years of age, had a tonsillectomy and adenoidectomy performed on July 28, 1931, and on Aug. 16, 1931, he developed a temperature and complained of a stiff neck. The following day his speech became nasal in quality, and there was difficulty in swallowing. At that time he was admitted to the hospital with a temperature of 101° F., pulse 146 per minute, and respiration 26 per minute. Physical examination and examination of the cerebrospinal fluid justified a diagnosis of acute anterior poliomyelitis with pharyngeal paralysis.

RECORD No. 196760.—R. L., male, 3 years of age, had a tonsillectomy and adenoidectomy on Nov. 13, 1935, and on Dec. 4, 1935, he became irritable, feverish, and vomited several times. On the following day his condition remained unchanged with the exception of the fact that he developed a stiff neck and stiff back. He was admitted to the hospital on December 9, at which time his temperature was 102° F., pulse 140 per minute, and respiration 40 per minute. Physical examination and cytoclinical examination of the cerebrospinal fluid established the diagnosis of acute anterior poliomyelitis. A few hours after entry the patient developed palatal paralysis, paralysis of both arms and the diaphragm. Death occurred on December 9.

PATIENTS WITH SPINAL POLIOMYELITIS

RECORD No. 205037.—E. F., male, 11 years of age, had his tonsils and adenoids removed on July 24, 1936, and on July 21, 1937, he complained of headache and developed a temperature of 103° F. On August 1 he was admitted to the hospital, at which time his temperature was 105° F., pulse 136 per minute, and respiration 32 per minute. His neck resisted anterior flexion, the back was stiff, the muscles were tender, the reflexes were hyperactive, and there was a positive Kernig sign. Examination of the cerebrospinal fluid showed chemical and cytologic changes consistent with those found in acute anterior poliomyelitis.

RECORD No. 142311.—A. G., male, 5¾ years of age, had his tonsils and adenoids removed on Aug. 25, 1930, and on Sept. 2, 1930, he became ill with headache, vomiting, stiff neck, stiff back, and hyperesthesia of his muscles. At the time of admission to the hospital, his temperature was 99.8° F., pulse 100 per minute, and respiration 24 per minute. Physical examination and examination of the cerebrospinal fluid supported a diagnosis of acute anterior poliomyelitis. At the time of discharge from the hospital the patient presented weakness of the left intercostal muscles as well as weakness of the right leg.

TABLE II

SPINAL POLIOMYELITIS IN RELATION TO TONSILLECTOMY AND ADENOIDECTOMY

Number of patients with spinal poliomyelitis with tonsils and adenoids present	184
Number of patients with spinal poliomyelitis with tonsils and adenoids previously excised	95
Number of patients with spinal poliomyelitis with tonsils and adenoids excised within 30 days prior to illness	8

TABLE III

BULBAR POLIOMYELITIS IN RELATION TO TONSILLECTOMY AND ADENOIDECTOMY

Number of patients with bulbar poliomyelitis with tonsils and adenoids present	40
Number of patients with bulbar poliomyelitis with tonsils and adenoids previously excised	74
Number of patients with bulbar poliomyelitis with tonsils and adenoids excised within 30 days prior to illness	17

Tables II and III indicate the number of cases of spinal and bulbar poliomyelitis in relation to the presence or absence of the tonsils and adenoids. The occurrence of eight cases of the former type and of seventeen cases of the latter type within a short period of time following the removal of the tonsils and adenoids is demonstrated in the following tables.

Table IV presents a tabulation of the number of cases of spinal poliomyelitis occurring within thirty days following the excision of the tonsils and adenoids. Although 287 patients with this form of the disease were admitted to the hospital, yet there were only eight patients with a history of a recent tonsillectomy and adenoidectomy, a percentage of 2.78. It will be further noted that of the eight pa-

TABLE IV

ACUTE ANTERIOR POLIOMYELITIS, SPINAL FORM, DEVELOPING WITHIN 30 DAYS FOLLOWING OPERATION

Total No. cases of spinal form = 287
No. cases following operation = 8
Percentage = 2.78

RECORD NO.	DATE OF OPERATION	DATE OF ONSET OF ILLNESS	DAYS BETWEEN OPERATION AND ONSET	CELL COUNT OF CEREBRO-SPINAL FLUID	PARALYSIS
205037	7/24/36	7/31/36	7	350	0
142311	8/25/30	9/ 2/30	8	17	+
154106	10/14/31	10/24/31	10	270	+
182418	8/13/34	9/ 7/34	24	210	0
214299	7/ 1/37	7/26/37	25	12	+
214691	7/22/37	8/18/37	26	62	+
138479	7/28/30	10/ 1/30	29	60	0
142785	8/29/30	10/ 1/30	30	90	0

TABLE V

ACUTE ANTERIOR POLIOMYELITIS, BULBAR FORM, DEVELOPING WITHIN 30 DAYS FOLLOWING OPERATION

Total No. cases of bulbar form = 131
No. cases following operation = 17
Percentage = 12.98

RECORD NO.	DATE OF OPERATION	DATE OF ONSET OF ILLNESS	DAYS BETWEEN OPERATION AND ONSET	CELL COUNT OF CEREBRO-SPINAL FLUID	PARALYSIS
108099*	8/11/27	8/21/27	10	63	+
62593	8/ 5/27	8/15/27	10	22	+
108514	8/14/27	8/25/27	11	180	+
162714	7/26/33	8/ 6/33	11	80	+
162675	8/16/32	8/28/32	11	101	+
153356	9/11/31	9/21/31	10	110	+
195745	9/ 1/35	9/14/35	13	39	+
191189	7/31/35	8/14/35	14	96	+
153131	9/ 2/31	9/16/31	14	180	+
142337	9/ 4/30	9/18/30	14	23	+
124487	8/ 3/31	8/17/31	14	120	+
172937	8/ 7/33	8/22/33	15	130	+
188272	8/28/35	9/13/35	16	95	+
109687	9/27/27	10/13/27	16	105	+
153511	8/21/35	9/ 8/35	18	49	+
152204	7/28/31	8/16/31	19	60	+
196760	11/13/35	12/ 4/35	20	166	Died

*This case had an adenoidectomy without tonsillectomy.

tients with the disease, only three developed it between the seventh and eighteenth day (the commonly accepted incubation period of poliomyelitis) following the operative procedure.

From Table V it can be seen that the number of cases of bulbar poliomyelitis occurring within thirty days following the removal of the tonsils and adenoids is in marked contrast to the number of cases of the spinal form following the same procedure. Of 131 patients with bulbar poliomyelitis admitted to the wards, seventeen or 12.98 per cent had had this operation performed within twenty days prior to the onset of their illness. Furthermore, fifteen of the seventeen patients developed the disease within the usual incubation period. Statistical computations demonstrate that the occurrence of this number of cases within the given period of time cannot be attributed to chance, nor can it be attributed to the usual frequency of poliomyelitis. The interval between the operation and the onset of both forms of the disease is indicated in Fig. 1.

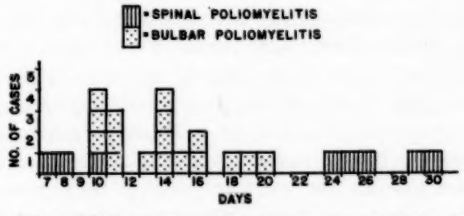

Fig. 1.—Interval between operation and onset of disease, in days.

Table VI, which demonstrates what might be called "scatter cases" (i.e., cases developing after a sufficient period of time has elapsed between the operation and the onset of the disease to indicate that the two conditions were unrelated), further emphasizes the concentration of the cases following operation as shown in Tables IV and V. One might reasonably include five of the cases listed in Table IV and two of the cases listed in Table V in this group.

TABLE VI

"SCATTER CASES" FOLLOWING TONSILLECTOMY AND ADENOIDECTOMY

Case 108932—	Developed	spinal	poliomyelitis	5 weeks	following operation
Case 194649—	Developed	spinal	poliomyelitis	6 weeks	following operation
Case 175114—	Developed	bulbar	poliomyelitis	7 weeks	following operation
Case 195734—	Developed	spinal	poliomyelitis	8 weeks	following operation
Case 196269—	Developed	spinal	poliomyelitis	12 weeks	following operation

It was thought that the type of paralysis occurring in the cases of bulbar poliomyelitis might bear some relationship to the presence or absence of the tonsils and adenoids. However, a study of Table VII does not confirm this impression. This may be due to the limited number of cases included in each group.

TABLE VII

DISTRIBUTION OF PARALYSIS IN BULBAR POLIOMYELITIS IN RELATION TO PRESENCE OR ABSENCE OF TONSILS AND ADENOIDS

BULBAR POLIOMYELITIS		
TONSILS AND ADENOIDS PRESENT	TONSILS AND ADENOIDS PREVIOUSLY EXCISED	FOLLOWING WITHIN 20 DAYS AFTER OPERATION
Pharyngeal 23 patients—57.50% Facial 6 patients—15.00% Respiratory 11 patients—22.50% Total No. patients—40	Pharyngeal 91 patients—77.00% Facial 13 patients—11.00% Respiratory 14 patients—11.80% Total No. patients—118	Pharyngeal 14 patients—77.8% Facial 3 patients—16.6% Respiratory 1 patient—5.5% Total No. patients—18

DISCUSSION

These clinical observations would give the impression that if the patient is harboring the virus at the time of the operation, traumatization of the tissues may enable it to gain entrance to the central nervous system either by way of the lymphatic system, the blood stream, or perhaps by direct neural extension. Furthermore, the high incidence of the bulbar form of the disease as compared with the spinal form suggested that it might be possible to reproduce this clinical condition in the monkey. However, suitable animal studies made in Dr. Lloyd Aycock's laboratory and under his direction produced uniformly negative results, as we were unable to produce the disease experimentally in monkeys by the direct inoculation of large amounts of a potent virus into either the tonsillar or peritonsillar tissues. The failure to reproduce the clinical condition in these animals may, however, be due to some anatomic difference between man and monkey and does not exclude tonsillectomy and adenoidectomy as possible factors contributory to the development of the infection in man.

The fact that one of the patients developed bulbar poliomyelitis following adenoidectomy (No. 108099, Table V) without tonsillectomy would indicate that it is not necessarily the latter operation that enables the virus to gain entrance to the central nervous system. This aspect of the problem, as well as the entire subject, requires further study before final conclusions can be safely made.

Abstracts of the patients included in this study are included.

We wish to acknowledge the helpful assistance of Dr. Lloyd Aycock of the Harvard Infantile Paralysis Commission, Harvard Medical School.

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2. Ayer, Wardner D.: Proceedings of Interstate Post-Graduate Medical Assembly of North America, 1928.

THE CONSTRUCTION OF AN EMERGENCY RESPIRATOR FOR USE IN TREATING RESPIRATORY FAILURE IN INFANTILE PARALYSIS

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ON FREQUENT occasions we have been asked to give directions for building respirators which would tide a patient over a day or a week, pending the arrival of a respirator of the type approved by the American Medical Association's Council of Physical Therapy.*

In Figs. 1, 2, and 3, constructional details of a wooden respirator which would answer such requests are given. The rubber collar is made by cutting a hole of suitable size from an inner tube of a moderate-size car.

The cover of the box is light and need not be hinged or fastened in any way (Figs. 1 and 3). The felt gasket is obtainable at any hardware store and is commonly used as weather stripping for leaky windows.

The vacuum pump shown at the right rear (Figs. 1 and 2) is the hand-size vacuum cleaner costing about $15.00 at any department store or electrical shop. The common household cleaners may pull a higher vacuum but are more expensive. The objectionable whining noise of the cleaner can be minimized by placing it in the next room and connecting it to the box by noncollapsible tubing (about 1 inch inside diameter). The length of tubing to be used should be determined by trial. If the tubing is too long, the cleaner cannot pull the required vacuum.

The observation window is made of double-thick (about ⅛ inch) window glass and should be about 6 inches square.

The frequency and depth of respiration are controlled by the hand-operated valve (Fig. 3), which is made from a piece of sole leather or of fiber. The valve hole in the box should be about 2 inches in diameter. If it is too small, the vacuum pump will maintain a slight negative pressure in the box, and then the patient cannot exhale easily. If the hole is too large, the valve will be difficult to work. This valve can be mechanized later by an experienced mechanic if the hand operation proves too arduous.

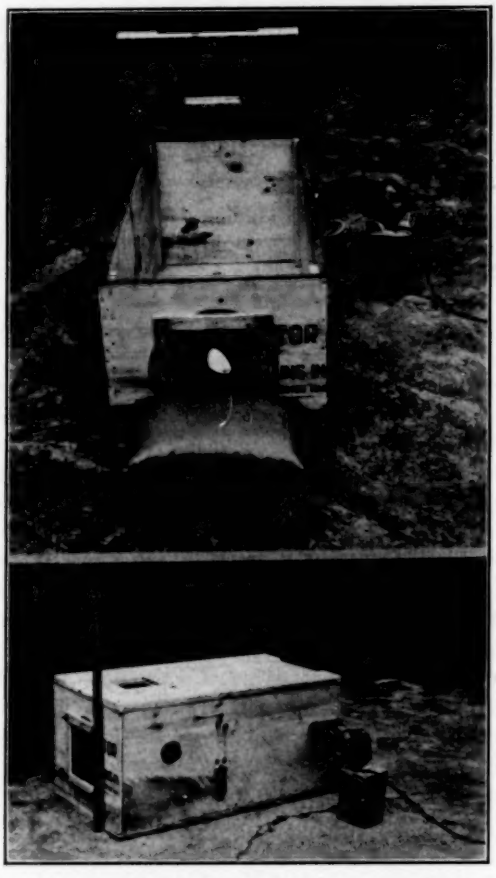
The pressure indicator may be a glass U-tube half full of colored water or a piece of straight glass tubing. If a U-tube is used, the arms should be about 12 inches to 15 inches long, while if a straight tube is preferred, it should be about that same length and dip vertically into a dish of water. One arm of the U-tube, or the upper end of the straight tube, should be connected by rubber tubing to the respirator box. A scale in

From the Harvard School of Public Health and Warren E. Collins, Inc., Boston, Mass.

*See J. A. M. A., May 9, 1931, p. 1580.

centimeters should be placed behind the manometer. The common type vacuum cleaner will lift water about 15 inches, although some cleaners are stronger. A vacuum of 8 inches (20 cm.) in the respirator box is probably the maximum that will ever be needed.

The dimensions of the box can be chosen to fit the patient, but the size of the head hole, viz. 9 inches, is important. The box in the illustration



Figs. 1 and 2.—Wooden respirator, 43 in. × 22 in. × 21 in., with vacuum cleaner attached at rear right and hand-operated valve.

was made from ½ inch packing box material at hand and could be duplicated by an experienced carpenter in about two hours. If there is any choice of lumber we suggest matched spruce, tongued and grooved, of ⅝ inch to ⅞ inch thickness. For children's-size machines, the lighter wood is ample. If the wood is not straight and leaky cracks result, they are best stopped with adhesive tape. No painting is necessary.

A patient is placed in the machine by lowering him into the box, bending up his knees, if necessary. One person then stretches the rubber collar, and either one or two persons lift the patient and push his head through until the shoulders touch the head end of the box, as in the approved type respirator. The collar is then stretched to suit. In general, it is best to have the collar hole a bit too large; and the resulting leaks around the neck may be stuffed with cotton. Otherwise the sharp rubber edge from a freshly cut inner tube may irritate the patient's neck.

The lid is then placed on the box, the vacuum cleaner started, and the valve moved back and forth by hand so that the patient breathes about fifteen times a minute at about 15 cm. negative pressure on the manometer. If the patient is badly cyanosed, deeper and quicker breaths can be given by manipulating the valve.

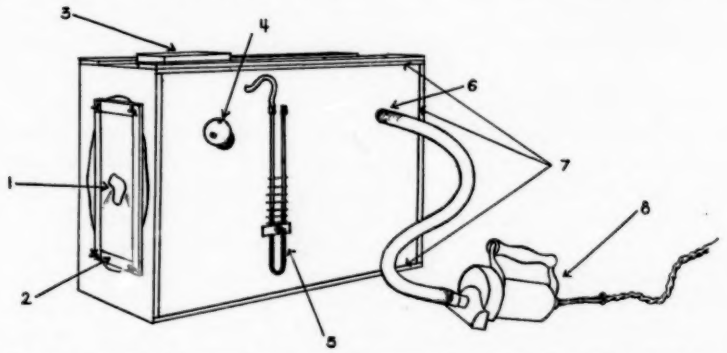


Fig. 3.—Measured perspective of wooden respirator. *1.* Rubber collar from inner tube 13 in. × 3 in. *2.* Collar frame fastened down with wing nuts on carriage bolts. *3.* Double-thickness glass window made tight with felt gasket. *4.* Valve port (2 in.) for hand-operable valve. *5.* U-tube manometer, 15 in. long, ¼ in. tubing. *6.* Hole, 1¼ in. *7.* Felt gaskets, tacked to frame. *8.* Vacuum cleaner.

A brief trial treatment on a healthy person, preferably a child, should be made by any group whose members have not used respirators. When the machine is running at about 15 cm. and 15 breaths a minute, speech will be interrupted when inhalation (negative pressure) is induced by the pump. Ask the subject to count out loud and the results will be evident immediately.

The objections to using such a makeshift apparatus are serious and perfectly definite. We have, therefore, misgivings in presenting this description. We would not offer the device for approval to the American Medical Association's Council of Physical Therapy. Nevertheless, when we receive emergency requests for help in building a machine for a few days' use, pending the arrival of a more satisfactory device, this is the type of equipment we recommend.

The objections to the emergency respirator are the following:

First, it is impossible to give any but small patients a semblance of the nursing care which is so vital in poliomyelitis. It is difficult to make the patient comfortable and to effect the postural changes so necessary in most patients with severe or even mild respiratory embarrassment. Even if the respirator works perfectly, it will not take the place of nursing care.

Second, such respirators made with the best cabinet-quality wood and by skilled cabinet workers have checked and cracked in an annoyingly short time. Such failure is probably caused by the rapid pressure changes and dampness within the respirator. It is, therefore, risky to use such a machine, put it in storage in the basement, and then expect it to be in working condition when the emergency arises. Theoretically, the wooden machines should last a long time. Practically, this has not proved to be the case.

MENTAL HYGIENE IN AN ORTHOPEDIC HOSPITAL

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THE problems of the management of prolonged convalescence are different from those of acute illness. As the acute stage passes and the patient enters the phase of recovery, the psychologic factors of the situation become increasingly important. It is so easy for the patient who is spending months at a time in bed to become discouraged and depressed. Even more significant is the ease with which such a patient develops selfish attitudes and lazy habits of thinking. These psychologic factors, rather than any physical defects, frequently form the primary basis of a patient's unwillingness or inability to resume a full and active life.

In children these factors are doubly important. The child's mind is extremely sensitive to suggestion, and the sheltered environment and limitation of activities necessary in any long convalescence are almost bound to have harmful effects unless careful precautions are taken. Most of these harmful effects are directly conditioned by the attitudes and behavior of adults surrounding the patient.

In the recent epidemic of poliomyelitis in Ontario attention was drawn to this aspect of treatment in a very dramatic way. Several hundred patients, most of them children, sustained paralysis which made it necessary for them to undergo a prolonged convalescence. This article describes the efforts which were made to reduce the seriousness of psychologic factors in such an epidemic.

CONVALESCENCE IN CHILDREN

Parents who are confronted with sudden serious illness in their child are naturally apprehensive. When this illness has the reputation of leaving the victim badly crippled for life, their feeling of anxiety is greatly heightened. An epidemic of "polio," for example, with its scare headlines and daily mounting toll of fatalities and paralysis is a terrifying experience for the parents of young children. The child himself when stricken with illnesses of this type cannot help but be influenced by the fear of his parents. This emotional attitude determines his behavior all the way through convalescence.

When the child recovers from the acute phases of the illness and begins to feel well in every respect, the necessity of physical restraint is bound

From the Department of Psychological Medicine of the Hospital for Sick Children and the Department of Paediatrics in the University of Toronto, under the direction of Alan Brown, M.D., F.R.C.P.(C).

to be irksome. Impatience, together with feelings of uneasiness concerning the prognosis, combine to make a situation fraught with emotional tension. The child is not sure of anything. He does not understand clearly why he must remain quiet for so long. Vague adult explanations are often incomplete and alarming. The talk of lameness when he feels so well is likely to be confusing.

Meanwhile the parents' anxiety makes them oversolicitous for the child and overattentive to his every need; this increased attention, coupled with his own immobility, creates a demand for entertainment. Anything that will amuse the child, keep him quiet and comparatively contented, is utilized. Very rapidly the child becomes more demanding, increasingly fond of being the center of attention, and finally a veritable egotistic despot. The fact that every trifling complaint is regarded seriously encourages him to overplay the invalid role. If he does not get his own way at once, he is likely to become emotionally upset and display heart-broken tears or else tantrums of anger. Such a situation, in short, tends to "spoil" the child. It is very difficult for him to keep his wholesome personality.

Poliomyelitis is an outstanding example of a disease in which such emotional factors are exceedingly important. Furthermore, the writers believe that many of the children who have apparently had this disease, have really had polioencephalomyelitis, in which there is usually widespread involvement of the central nervous system. The possibility of organic damage to those centers in the brain which have to do with emotional control must therefore be considered. This is probably an additional factor accounting for the difficulty that many convalescent children have in controlling their tempers and their behavior. Some children of this type show very little else in the way of sequelae and, superficially, seem to have recovered completely. This makes it all the harder for such children to understand the necessity of even a short convalescence. Usually they have little insight into their emotional instability.

THE ONTARIO ORTHOPEDIC HOSPITAL

During the late summer and early autumn of 1937, an epidemic of poliomyelitis of primary importance swept through Ontario. In all 2,635 people were affected, and of these over 1,000 sustained paralysis sufficiently severe to warrant careful orthopedic treatment. In order to carry out this treatment, it was necessary in the majority of cases for the patients to be flat on their backs (usually on Bradford frames) for many months. At the beginning of the treatment it was not known exactly how long this physical restraint would have to be continued, but in some cases at least it was estimated that it would be six to eighteen months or even longer. In order to rest weakened or paralyzed muscles, the affected limbs were placed in special splints. Physiotherapy and good nursing care completed the physical aspects of the treatment.

The Provincial Department of Health in Ontario wished to make certain that every child paralyzed as a result of this epidemic would have a good start along the road to recovery. The department therefore undertook to supply, free of charge to all who wished, a short period of hospital treatment. The hospital arrangements varied according to the needs of the community. In Toronto, where the concentration of cases was greatest, the Department of Health took over a hospital building which had been used for several years as a nurses' residence;* and within a few days equipped it completely as an orthopedic hospital. The full details of this project are published elsewhere.† The chief purpose was to provide each child with at least three weeks' treatment in a carefully controlled environment. During this time the child was properly fitted with a Bradford frame and splints if necessary. Suitable physiotherapy was given. It was decided that the three weeks' stay in the hospital was sufficient to train the children to become accustomed to this treatment so that the regimen could be continued efficiently at home. In order to ensure this, the mothers of the children were brought into the hospital and carefully instructed as to the correct way of nursing and massaging the patients. Instruction was given by means of lectures, demonstrations, and practical work under supervision. It took place during the two days prior to each child's discharge.

The first children to be admitted to the hospital arrived on Sept. 27, 1937, and they were discharged in groups ranging in numbers from eight to twenty-four, twice weekly beginning three weeks later. The last group was discharged on Dec. 8, 1937. During the ten weeks in which the hospital was open, 283 children received treatment and training. The age and sex distributions of these children are shown in Table I. There were more boys than girls and nearly one-half (46 per cent) of the children were under six years of age. Many young adults were treated in the general hospitals of the city, and many patients were kept at home under the care of their family doctors. These figures, therefore, do not give a complete picture of the extent of the epidemic in Toronto. Of the children treated in the Orthopedic Hospital, 218 came from Toronto or the immediate environs. The other 65 came from widely scattered points in the province.

TABLE I

AGE (YR.)	BOYS	GIRLS	TOTAL
0- 3	20	20	40
3- 6	48	41	89
6- 9	40	23	63
9-12	23	18	41
12-15	15	19	34
15-18	15	1	16
	161	122	283

*The Grace Hospital, College and Huron Streets, Toronto.

†Report on Poliomyelitis in Ontario, 1937, published by authority of the Minister of Health, Toronto, Ontario, March, 1938.

Responsibility for the medical and surgical treatment of these children was given to the staff of the Hospital for Sick Children, Toronto. The supervision of their mental health was at once recognized as an important part of the general medical care. The recognized purpose of the Orthopedic Hospital was not only to minimize the extent of physical crippling, but also to prevent the development of any mental crippling. A detailed mental hygiene program was carefully prepared. The Deputy Minister of Health for Ontario collaborated in this project and through his generous support the plan as described below was put into action.

THE MENTAL HYGIENE STAFF

The mental hygiene staff consisted of a neurologist, psychiatrist, and psychiatric social worker from the Department of Psychological Medicine of the Hospital for Sick Children, together with four occupational therapists provided by the Provincial Department of Health. Friends or relatives were not allowed to visit the children because of the danger of concurrent infections. For this reason the early evenings, Saturdays, and Sundays might have been trying times. However, there was a sufficiently large full-time staff to enable two or three aides to be on duty during these times and at all other times when the children were not either busy with routine medical and nursing procedures or asleep.

The program in its final form would have been difficult had it not been for the voluntary assistance of many workers, including librarians, teachers, artists, and occupational therapy students. At one time the number of voluntary assistants, spending a definitely assigned time each week in the hospital, was over twenty.

THE WARDS

Two floors of the hospital were thrown open to patients. The wards were small, the largest having space for nine patients and the smallest, for only one or two. There were fourteen such wards on each floor. For several weeks an additional ward containing over thirty beds was also used. While everything was perfectly clean, it must be remembered that the building was old. The lighting in many of the wards was poor, and the walls were dull and unattractive. One of the first tasks was to brighten the atmosphere of the wards. Colorful posters were donated by the various travel agencies and foreign consulates in the city and were fastened high on the walls so that they could easily be seen. Later many of these were replaced by even more colorful pictures made by the children themselves.

The lack of adequate lighting presented a serious problem which was never completely solved. The danger of eyestrain in children who had to lie for long periods on their backs seemed to be a real one, especially when they tried to read in this position. In a few of the darker wards,

however, suitable lamps were attached to the walls to provide indirect illumination of the correct intensity.

The number of small wards made the grouping of children relatively easy. Nevertheless the rapid turnover made the hospital population anything but static, and it was hard to keep any one ward limited to one particular type of child. In so far as it was possible, the children were arranged according to their age groups, as well as according to their sex and the extent of their disability.

PLANNED ACTIVITIES

The basic principle of the program of activities was very simple. It was decided that nothing would be included in the program which did not have positive, constructive, and, as far as possible, permanent value for the children. In other words, there was little place for that sort of entertainment which is merely amusing or exciting. Granted that the visit of the clowns from the indoor circus was a delight to both children and staff, such entertainment was not considered to be sufficiently constructive for a regular place on the long-term program.

Music.—Through the courtesy of radio manufacturers, twelve radios were lent or donated to the hospital. These were distributed among the older children's wards. In addition to the radios, two large phonographs and one portable phonograph were donated privately. An electrical company lent three record-players which could be attached to the radio loud speakers. With this equipment an excellent musical program was worked out.

It was realized at the outset that it would be a mistake to have the radios on all the time. This would be distracting and fatiguing. At certain times the children could select their own programs, but usually they were guided in their selection. Such programs as the Children's Symphony Hour with Walter Damrosch were featured. In addition to encouraging them to listen to good music, an effort was made to build up their musical background and help them to develop an interest in all aspects of music. Books were provided which told about the composers, the stories of the operas, etc. Interest was further fostered by the playing of many fine records which were purchased especially for the purpose.

Singing was an important part of the musical program. No matter how badly disabled a child may have been, he could always sing (or try to). Simple songs were taught to the younger children, while part songs were attempted by the older ones. Rhythm bands were organized among the younger children. The instruments were merely cheap rattles or homemade noisemakers, but the skill in their use acquired by some of the children was amazing.

Reading.—The problem of reading was a difficult one. All the children had to remain on their backs, most of them without a pillow.

Many of them had both arms in splints, and therefore could not hold a book or turn pages. As an emergency measure a stock model bed tray with an elevating top was adapted by making one or two minor changes. Reading material could be clamped securely to the top, and then held in position over the patient's head so that the text could be read easily.

The Toronto Public Library lent the hospital over one hundred books. The Junior League and other private agencies donated nearly two hundred more. By the time the hospital had been open two weeks, an excellent library was available, containing books suitable for children of all ages. It was often difficult to get the children to start reading. Most of them preferred the comics sent from home. These, with their small indistinct print and frequently fantastic plots, were but poor substitutes for good books. However, once the child developed an interest in a story or a book, it was relatively easy to keep him going. The volunteer librarians were a great help in this field. All the children loved having stories read to them. Often one child in a ward would undertake the responsibility of reading a story or even a full length book to the others. Sometimes the children in a ward would read a play, each child taking a different part. This seemed to bring unusual satisfaction. Some of the younger children actually made a start toward learning how to read, partly because of stimulation from the other children, partly because of the books provided, and partly by means of the various alphabet games which were available. The educational and cultural value of this part of the program was unlimited. Many of the children asked for their school books. No formal teaching of school work was attempted because the children were not in the hospital for sufficient length of time to warrant it. Nevertheless, by encouraging the reading of books which had some relationship to their school studies, the children maintained their interest in school. A teacher, assigned to the hospital as liaison officer by the local Board of Education, organized the extramural teaching of the children after they were discharged.

Motion Pictures.—A moving picture projector was borrowed from the Department of Psychology, University of Toronto, for the whole time that the hospital was open. After experimenting with one or two short films of the cartoon and comedy variety, it was obvious that this type of entertainment was too exciting and stimulating to be good therapy. Finally, however, some excellent nature films were borrowed from the provincial government. These proved to be valuable in many ways. They stimulated conversation about the nature and habits of animals and led many of the children to seek more information in reference books. Particularly valuable were the colored travel films, lent by several interested physicians. Great interest in geography and history was engendered by these pictures. Such remarks as, "they didn't tell us at school that they had such modern looking houses in Oslo!" were typical.

The films were shown to the older children three or four times a week, usually in the early evenings. It was discovered that if the pictures were projected high on the cream-colored walls near the ceilings, all the children could see perfectly without straining their eyes or moving their heads. Very little shifting of the beds was required in order that all could have a clear view.

Occupational Activities.—The occupational therapists showed great initiative in adapting their usual type of craft and occupational work to the special difficulties of these convalescent children. For example, suitable occupations had to be devised for the large number of 2- and 3-year-old patients. The program finally developed was surprisingly varied. Peg boards, blocks, large beads which could be threaded on a shoe string, and a wide assortment of toy animals and dolls were used for the very young patients. Balloons and toy airplanes strung up overhead were a special source of joy and interest. Cutting and pasting, leather work, weaving, sewing, knitting, making puppet heads and dresses, and making plasticine models were activities frequently seen among the older children.

Creative Activities.—The hospital had not been open long before some of the teachers from the Children's Art Center of the Art Gallery became interested in the work. They, with the assistance of graduates of the College of Art, were most generous with their time.* The timetable was arranged so that every child more than 4 years old had at least two periods a week of creative art. This included not only drawing and coloring pictures, but modeling, cutting figures from colored sheets of paper, and assembling all sorts of artistic projects such as miniature circuses, parades, etc. Even those children with both arms in splints could look on and offer advice and criticism. They were usually given some title to dignify their position, such as "Chairman of the Advisory Board" or "Chief Inspector and Critic of Art."

Free Time.—With all this program in action, one might wonder if the children did not have too much to do, too much stimulation, and far too much fuss made over them. This danger was foreseen at the start. The children's daily routine called for a two-hour rest period immediately after the midday meal. This rest period was carefully enforced. Blinds were drawn, windows opened, and both patients and nurses encouraged to be as quiet as possible. Most of the children slept during this time. In addition to this rest period each child had time during the day when he was left to his own devices. He was encouraged to do anything he wished, except call for help and attention. In this way a beginning was made towards the development in these children of some measure of independence.

*Acknowledgement is gratefully made to Mr. Arthur Lismer and Mr. J. deN. Kennedy for their interest and help in making the art program possible.

MENTAL HYGIENE WORK

The Children.—Every child more than 4 years old was seen by the psychiatrist or the psychiatric social worker, either during admission or as soon as possible afterwards. This interview was felt to be very important since in a five- or ten-minute chat it was possible to make the child feel that some one at the hospital was taking a special interest in him. The reason for the child's coming to the hospital, the nature of his disability, and the rationale underlying the prescribed treatment were explained in simple terms. If possible, he was told the approximate length of his stay. The fact that there could be no visitors was made quite clear, and the reason for this rule was explained. This first interview usually closed with a brief description of the sort of proceedings and activities which the child might expect at the hospital.

During subsequent interviews the child was made to understand that his convalescence must necessarily be prolonged. The same sort of treatment he was receiving in the hospital must be continued at home. There would be no skating or climbing fences that winter. Most of the older children wanted to know the chances of a complete cure, with return of power to the weakened muscles. These questions were always answered truthfully by saying that it was impossible to tell at the moment and that improvement took place slowly but steadily, sometimes for many months. The problem of the future gave the younger children no concern whatever. These talks with the children were always made as cheerful and optimistic as possible. It was pointed out that they would now have the opportunity to learn to do all kinds of interesting things at home, things they never had time to do before.

Occasionally children with emotional problems of one kind or another were found. There were several severe cases of homesickness. The commonest psychologic factor here was an abnormally strong attachment to the mother plus the fact that the child, in most cases, had never been away from home before, even for one night. There were several children who were emotionally unstable, showing either excessive crying or unusual lability of mood and excitability. Reassurance, cheerfulness, and gentle firmness usually helped the child to regain his self-control and sense of security.

The different types of paralysis in the children made individual work almost obligatory. The problem presented by a boy with paralysis of both legs was different from that of the girl who could move her legs but whose arms were completely useless. The latter type of child, however, could always participate in conversation, singing, and listening.

Work with the Nurses.—Naturally a program as intensive as this could not be attempted without gaining the full understanding and cooperation of the nurses. At the beginning of the project the nurses were assembled and the significance of the psychologic factors was fully ex-

plained to them. The proposed activities were outlined, and the necessity for maintaining an objective and optimistic attitude towards the children was urged. It was pointed out that the danger lay in allowing one's natural sympathies to get out-of-hand. The importance of helping these convalescent children to develop wholesome habits of behavior was emphasized.

Close contact with the work of the nurses was constantly maintained. Children with problems in behavior or adjustment were referred by them from time to time. Such children were usually interviewed privately. The problem was then discussed with the nurse, and a method of dealing with the situation was worked out. On several occasions, towards the end of the hospital project, the nurses handled situations of this kind themselves with admirable results. The interest shown by the nurses in the whole program was very gratifying.

Work with the Parents.—During the two-day training period for the parents time was set aside for an informal lecture and discussion on the important general principles underlying the subsequent training of the child at home. The dangers of too much sympathy and too much spoiling were pointed out. The importance of routine, of good habits of eating, sleeping, and elimination, and of consistent discipline was stressed. In order to make sure that the most important points were remembered, a multigraphed booklet was prepared for the parents. This contained instructions and suggestions calculated to be of help in looking after the children at home. In the discharge ward the parents were shown in detail how to help the child carry on many of the interesting things he had learned to do in the hospital. Displays of suitable books, games, occupational and creative material were set up, keeping in mind the fact that most of the homes to which the children would return were either in marginal financial circumstances or on relief.

As the work developed, more and more visiting nurses and social workers from various city and provincial organizations began to come to the lectures. Often there were more workers present than parents. The visiting teacher assigned to the hospital, being fully acquainted with the problems involved in the convalescent care of these children, was in a unique position to follow these children after they went home and to supervise their education. She made arrangements with those parents who had children of school age to visit their homes in order to carry on educational work.

THE FOLLOW-UP

The average stay of the children in the Orthopedic Hospital was a little over three weeks. On discharge most of them returned to their homes under the care of their parents. A few, who for one reason or another could not be cared for properly at home, were transferred to a special ward in the Toronto hospital for infectious diseases. The follow-

up was in charge of the local, municipal, and county departments of health. In most centers special public health nurses were assigned to make frequent visits. Cooperating with the nurses were the visiting teachers, and physiotherapists. The local service clubs and the Ontario Society for Crippled Children provided reading racks and other materials where necessary. They also arranged to bring the children back to the Hospital for Sick Children at stated intervals for orthopedic and neurologic examinations.

RESULTS

The difficulty of appraising the results of this mental hygiene program is obvious enough. Mental health and wholesome attitudes are attributes which are not easy to measure quantitatively. By observing the change in the children during their three weeks' stay, however, and by observing them again on their return to the Hospital for Sick Children for re-examination, the writers were left with little doubt as to the efficacy of the measures employed. They were strikingly successful. This was reinforced by the spontaneous remarks and comments made by the many physicians who visited the Orthopedic Hospital and saw the program in action. It was further reinforced by the information obtained through informal chats with the parents when they returned with their children for re-examinations.

In the first place the hospital itself was an unusually cheerful place. There was never any effort to keep the wards very quiet except during the rest periods, and at certain times of the day shouting, laughing, and singing could be heard from almost all wards. The second noticeable feature was the spirit of unselfishness and the desire to help one another that was so frequently seen among the children. The third characteristic which was not so obvious to the casual observer but which was perhaps more important than the first two was the willingness to learn and the spirit of cooperation which these children developed. The visiting teachers reported later that never had they taught a more enthusiastic and interested group of children than those who had been in the Orthopedic Hospital. The following case summary is only one example of many that could be cited:

J. B., aged 13 years, an intelligent, attractive girl who lived in a small town thirty miles from Toronto, contracted a "cold" early in September. Within twenty-four hours her four limbs were completely paralyzed. There was also some involvement of her intercostal and back muscles. On the third day she was transferred to the Hospital for Sick Children because it was felt that she might need the respirator at any time. She survived the acute stage, however, without the "iron lung." She was placed on a Bradford frame, with splints applied to immobilize her four limbs. About this time (sixteen days after the onset) she became very depressed and homesick. It was the first time she had ever been away from home. She also became increasingly irritable and difficult to nurse. She kept demanding to be allowed to go home. Her crying and her tempers upset the other children in the ward.

When the Orthopedic Hospital was opened, she was one of the first to be admitted. The psychiatrist chatted with her and allowed her to tell all her complaints in detail. She explained that she knew the doctors had lied to her. They had promised her that she would go home in two weeks and here it was nearly three. She knew they had lied to her about her paralysis, too. She was convinced that she would never be able to walk again.

Some time was taken to explain exactly what was going to happen at this new hospital and how the staff were really counting on her help to maintain cheerfulness in the ward. As soon as possible she was informed of the exact date of her discharge. Something of the girl's problem was explained to the nurses, and they took a special interest in her for a few days. By this time the other factors, such as the infectious cheerfulness and the full program of activities, had begun to take effect. She responded very well. She and a few other girls of about her own age developed little games they could play. Finally a small play was organized. She was particularly interested in stories which were read to her at first. Finally she achieved a technique so that she could read a book and turn the pages herself, using one of the reading stands.

After nearly five weeks she went home with her mother—a radiantly happy and cheerful girl. Contact was maintained by correspondence, and a steady improvement in her muscle power took place. Six months later (March, 1938) she returned to Toronto for re-examination. This showed marked improvement in all limbs except the left leg. However, her chances of being able to walk with the aid of some sort of brace were excellent.

Her mother stated that she maintained her cheerfulness and unselfishness at home. She has been working hard at her studies with the help of one of the teachers from the high school. One of the chief items of interest, however, was the fact that she had been responsible for the organization of a troup of Girl Guides among the friends she had made at the Orthopedic Hospital. This was accomplished entirely by correspondence.

The girl's attitude to herself and her illness is as fine as could be desired. She is optimistic and is not afraid. Her illness will not leave her with psychologic and emotional distortions.

The program in psychologic medicine introduced into the Ontario Orthopedic Hospital served a twofold purpose. Primarily organized to give the younger patients guidance in adjusting to a prolonged convalescence, the hospital was also used as a demonstration center. The results obtained, therefore, are not to be judged by the effect on the children alone. Physicians and nurses from all over the province were frequent visitors. The parents of the patients received instruction not only in physical management of the paralyzed patient, but also suggestions whereby psychologic problems could be anticipated and met. At the conclusion of the work in psychologic medicine carried out in this hospital, it was felt that the effort expended had produced a beneficial result.

DRUGS TRANSMITTED THROUGH BREAST MILK

II. Barbiturates

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IN CONTINUATION of our study on drugs transmitted through breast milk[1] we proceeded with the barbiturates and submit here the results.

The literature contains very little in regard to barbiturates in connection with breast milk. Frensdorf[2] gave an epileptic woman 0.1 gm. of phenobarbital three times daily for a few days before and after labor. Her child, normal at birth, became gradually more and more sleepy but recuperated after the mother discontinued the drug. This would point to transmission although no chemical analysis of the milk is reported to confirm the passage of the drug in the milk.

Kwit and Hatcher,[3] on the other hand, gave barbital to each of two women in a dose of 325 mg. and to each of two others in a dose of 650 mg., and no evidence could be found of the presence of barbital in any specimen of milk.

EXPERIMENTAL

Patients in the maternity ward of Temple University Hospital having babies at the breast were used as subjects in this study. Four series were run using phenobarbital U.S.P. and phenobarbital sodium U.S.P. with each drug subdivided as to sedative and hypnotic effects.

During the first five days following delivery no medication in any form was given to either the mother or the nursling used in these tests. Following the administration of the drug, one-half ounce of milk was collected at each of the feedings during each day (6 A.M., 10 A.M., 2 P.M., 6 P.M. and 10 P.M.) and pooled for chemical analysis.

The chemical test used was that described by Beal and Czalkowski[4] in which the phenol group is converted into m-nitrobenzoic acid by heating with sulfuric acid and potassium nitrate. The reaction mixture is then made alkaline with ammonium hydroxide and reduced with ammonium sulfide. The m-diamino compound is formed with the production of a reddish-brown ring which diffuses through the liquid to an orange color. The ammonium sulfide is added without mixing, in order to produce the ring.

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Samples of milk from mothers having no drug were negative, and samples (2 oz.) to which ½ grain of phenobarbital had been added gave positive reactions with this test. One-half ounce of milk was used in making the chemical test, thus detecting phenobarbital when present to the extent of ⅛ grain in the sample used. These served as controls for the application of the test on samples of milk tested in the series. The procedure of the drug administration will be described in connection with each series.

Series 1 consisted of 10 patients using phenobarbital. Beginning on the morning of the sixth day after delivery, one tablet containing ½ grain of phenobarbital (average dose) was administered to the mother by mouth at 7 A.M., 11 A.M., 3 P.M., and 7 P.M. Thus a total of 2 grains was given each day until the patient was discharged from the hospital.

Observations were made on mother and child as to the sedative effect of the drug, as well as effect on respiration, gastric disturbances, skin rashes, effect on temperature, and any unusual symptoms.

TABLE I

PHENOBARBITAL—SEDATIVE EFFECT

SUBJECT	USE OF SEDATIVES BEFORE ADMISSION	NO. DAYS RECEIVED DRUG	GRAINS PER DAY	CHEMICAL TESTS		SYMPTOMS	
				POSITIVE	NEGATIVE	MOTHER	CHILD
M. D.	None	4	2	3	1(2)	None	None
H. S.	None	5	2	4	1(3)	None	None
H. L.	None	4	2	3	1(3)	None	None
R. S.	None	4	2	1(2)	3	None	None
F. G.	None	1	2	0	1	None	None
A. W.	None	4	2	1(3)	3	None	None
E. G.	None	4	2	1(2)	2	None	None
J. K.	None	4	2	3	1(4)	None	None
G. B.	None	4	2	4	0	None	None
M. S.	None	4	2	3	1(2)	None	None

A total of thirty-seven day-samples having been collected, a positive reaction was obtained in 23 cases (62.16 per cent) and negative reaction in 14 (37.84 per cent). Of the 10 cases, 6 (60 per cent) showed more positive specimens than negative specimens (Table I). The small number in parenthesis refers to the day of drug administration when the exception was noted. No clinical evidence of transmission was noted in any case.

Series 2 consisted of 10 patients using phenobarbital; the hypnotic effect on mother and child was noted. The only change in procedure was to administer to the mother one tablet containing 1½ grains of phenobarbital at bedtime on the evening of the fifth day after delivery, and this was continued each night until the patient was discharged.

A total of forty day-samples having been collected, a positive reaction was obtained in 32 cases (80 per cent) and negative reaction in 8 (20 per cent). Of the 10 cases, 9 (90 per cent) showed more positive

specimens than negative specimens, the other case being 50 per cent positive (Table II). The small number in parenthesis refers to the day of drug administration when the exception was noted. Only in the last case (E. B.) were any clinical symptoms manifest, as noted. The evident of rash on the child before drug administration cannot be deduced as being caused by the drug even though present the first day of the test.

TABLE II

PHENOBARBITAL—HYPNOTIC EFFECT

SUBJECT	USE OF SEDATIVES BEFORE ADMISSION	NO. NIGHTS RECEIVED DRUG	GRAINS PER NIGHT	CHEMICAL TESTS		SYMPTOMS	
				POSITIVE	NEGATIVE	MOTHER	CHILD
F. V.	None	4	1½	4	0	None	None
A. M.	None	4	1½	3	1 (1)	None	None
G. H.	None	4	1½	4	0	None	None
R. R.	None	3	1½	2	1 (1)	None	None
L. M.	None	4	1½	3	1 (1)	None	None
S. W.	None	4	1½	3	1 (2)	None	None
M. W.	None	4	1½	2	2 (1, 4)	None	None
M. D.	None	4	1½	4	0	None	None
C. S.	None	5	1½	3	2 (1, 5)	None	None
E. B.	None	4	1½	4	0	Temperature 103.2° F. 1st day. Herpes on lips 3rd day.	Rash 2 days preceding drug and only 1st day of drug.

Series 3 consisted of 10 cases and repeated Series 1 for the sedative effect; phenobarbital sodium was used in this series.

TABLE III

PHENOBARBITAL SODIUM—SEDATIVE EFFECT

SUBJECT	USE OF SEDATIVES BEFORE ADMISSION	NO. DAYS RECEIVED DRUG	GRAINS PER DAY	CHEMICAL TESTS		SYMPTOMS	
				POSITIVE	NEGATIVE	MOTHER	CHILD
F. S.	None	4	2	3	1 (4)	None	None
M. S.	None	5	2	5	0	None	None
M. B.	None	4	2	2	2 (1, 4)	None	None
A. O.	None	4	2	3	1 (4)	None	None
G. D.	None	3	2	2	1 (1)	None	None
M. M.	None	4	2	3	1 (2)	None	None
C. Z.	None	4	2	0	4	None	None
M. G.	None	4	2	2	2 (1, 3)	None	None
A. Y.	None	4	2	4	0	None	None
A. W.	None	4	2	3	1 (1)	None	None

A total of forty day-samples having been collected, a positive reaction was obtained in 27 cases (67.5 per cent) and negative reaction in 13 (32.5 per cent). Of the 10 cases, 7 (70 per cent) showed more positive specimen than negative specimens, 2 of the remainder showed 50 per cent positive, and only 1 was entirely negative (Table III).

The small number in parenthesis refers to the day of drug administration when the exception was noted. No clinical evidence of transmission was noted in any case.

Series 4 consisted of 11 cases and repeated Series 2 for the hypnotic effect; phenobarbital sodium was used in this series.

TABLE IV

PHENOBARBITAL SODIUM—HYPNOTIC EFFECT

SUBJECT	USE OF SEDATIVES BEFORE ADMISSION	NO. NIGHTS RECEIVED DRUG	GRAINS PER NIGHT	CHEMICAL TESTS		SYMPTOMS	
				POSITIVE	NEGATIVE	MOTHER	CHILD
M. M.	None	4	1½	3	1 (3)	None	None
E. T.	None	4	1½	4	0	None	None
P. C.	None	4	1½	3	1 (2)	None	None
R. B.	None	5	1½	3	2 (1, 5)	None	None
M. Cr.	None	5	1½	5	0	None	Hypnotic effect on 8th & 9th days. Sleepy and hard to awaken.
H. V.	None	5	1½	3	2 (4, 5)	None	None
C. H.	None	3	1½	2	1 (2)	None	Seemed toxic. Slept all the time, quite hard to awaken.
E. M.	None	4	1½	3	1 (4)	None	None
S. R.	None	4	1½	3	1 (2)	None	None
A. D.	None	5	1½	3	2 (2, 3)	None	None
M. Ch.	None	4	1½	3	1 (2)	None	None

A total of forty-seven day-samples having been collected, a positive reaction was obtained in 35 cases (74.47 per cent) and negative reaction in 12 (25.53 per cent). The 11 cases (100 per cent) showed more positive specimens than negative specimens (Table IV). The small number in parenthesis refers to the day of drug administration when the exception was noted. Two cases showed definite clinical evidence

TABLE V

DRUG	CHEMICAL TESTS ON SAMPLES OF MILK		CASES IN WHICH MAJORITY WERE		TOTAL CASES SHOWING TRANSMISSION PER CENT	CASES OF CLINICAL EVIDENCE
	POSITIVE PER CENT	NEGATIVE PER CENT	POSITIVE PER CENT	NEGATIVE PER CENT		
Phenobarbital (sedative)	62.16	37.84	60.0	40.0	90.0	0
Phenobarbital (hypnotic)	80.00	20.00	90.0	0.0	100.0	0
Phenobarbital Sodium (sedative)	67.50	32.50	70.0	10.0	90.0	0
Phenobarbital Sodium (hypnotic)	74.47	25.53	100.0	0.0	100.0	2

of the transmission of the drug with resulting symptoms of hypnotic effect, with deep slumber attended by some difficulty in awakening.

SUMMARY AND CONCLUSIONS

Barbiturates when administered to a lactating mother are transmitted by breast milk, as shown by chemical analysis.

Analyses of individual specimens of milk after administration of barbiturates in ½ grain doses at stated intervals, although amounting in the aggregate to 2 grains in a day, do not show as high a percentage of positive reactions as do similar specimens after the administration of 1½ grains at bedtime. Thus, concentrated doses seem to have more effect on transmission than do cumulative doses.

The individual cases show the same relationship as the individual specimens.

In only two of the forty-one cases was there any clinical evidence in the child, and thus there is the possibility that the child may be affected by the breast milk after medication of the mother with barbiturates. In this series the possibility is about 5 per cent and occurs in the hypnotic group.

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DRUGS TRANSMITTED THROUGH BREAST MILK

III. Bromides

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A THIRD part of our study on drugs transmitted through breast milk[1] consists of a series during the administration of sodium bromide to the lactating mother.

Holt[2] states that bromides, when long administered, may be eliminated in sufficient quantity to produce their constitutional effects on the child. Morse[3] mentions bromides as being transmitted through breast milk. Griffith[4] states that bromine passes into the milk to some extent and occasionally in such a way as to affect the infant seriously. Kwit and Hateher,[5] after studying a number of drugs, found that none of them except sodium bromide was present in the milk in an amount sufficient to indicate that the continued use of such milk would injure a normal nursing child. After administering sodium bromide in single doses of 1 gm. and total doses of 15 gm., every specimen of milk, except the first in one case, and the first and second in another, yielded bromide.

Bucura[6] also definitely demonstrated bromides in breast milk. Van der Bogert[7] reported a case in a 6-month-old nursling in whom a painful papulopustular eruption occurred. The mother had been taking a bromide preparation for some time, and the breast milk contained more than traces of bromide.

Our tests were carried out to ascertain whether or not the clinical evidence of transmission of bromides would be confirmed by chemical analysis of the breast milk during the course of administration of the bromide to the lactating mother.

EXPERIMENTAL STUDIES

Patients in the maternity ward of Temple University Hospital having babies at the breast were used as subjects. During the first five days following delivery, no medication in any form was given to either mother or nursling used in these tests.

Beginning on the morning of the sixth day following delivery, one fluid dram of sodium bromide in peppermint water (average dose, 15 grains of sodium bromide in each fluid dram) was administered to the

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mother. This was repeated every four hours (6 A.M., 10 A.M., 2 P.M., 6 P.M., 10 P.M., and 2 A.M.), and the medication continued each day until the mother was discharged from the hospital.

Observations were made on both mother and child as to the sedative action of the bromide, effect on respiration, gastric disturbances, skin rashes, effect on temperature, and any unusual symptoms.

At each feeding during the twenty-four hours, one-half ounce of breast milk was collected and pooled for analysis.

One ounce of breast milk was heated to coagulate the proteins and filtered. The filtrate was acidified with dilute sulfuric acid, a few drops of concentrated nitric acid were added, and carbon bisulfide was used as the solvent for any bromine liberated, a positive test resulting in a brown color. Three fluid drams of the bromide solution in peppermint water when added to 2 ounces of breast milk and 1

TABLE I

SODIUM BROMIDE—SEDATIVE EFFECT

SUBJECT	USE OF SEDATIVES BEFORE ADMISSION	NO. DAYS RECEIVED DRUG	GRAINS PER DAY	CHEMICAL TESTS		SYMPTOMS	
				POSITIVE	NEGATIVE	MOTHER	CHILD
A. G.	None	4	90	3	1 (4)	Not as nervous, slept well but not drowsy.	Less irritable
A. F.	None	4	90	4	0	Rested comfortably, slept well, not drowsy.	Less irritable
G. M.	None	4	90	4	0	Papulopustular rash on face, neck and other parts of body. Felt well, slept well, no drowsiness.	Rested quietly, did not cry frequently.
M. La.	None	4	90	4	0	Very drowsy, slept practically all the time.	Very drowsy, did not cry when disturbed. Slept continually but nursed well.
J. C.	None	4	90	4	0	No unusual symptoms. Rested and slept comfortably.	Less irritable.
M. P.	None	4	90	4	0	No unusual symptoms. Rested and slept comfortably.	Seemed sleepy. Not irritable. Rested quietly.
M. Le.	None	3	90	3	0	No unusual symptoms. Rested quietly.	Less irritable.
V. D.	None	4	90	4	0	Less irritable.	Less irritable.
J. Ch.	None	3	90	3	0	Less irritable.	Less irritable.
R. G.	None	5	90	4*	0	Papulopustular rash on face and neck.	Slight rash on face for 2 days.

*One sample lost due to breaking of bottle.

ounce of this prepared milk used for a control test gave positive evidence of bromide. The amount added to the control specimen represented 45 grains of bromide, or half the amount administered to the subject, and gave 22.5 grains in the amount taken to test.

Ten subjects were used in this series as shown in Table I.

A total of 38 specimens of milk were analyzed and 37 (97.37 per cent) gave positive results; only 1 (2.63 per cent) was negative, and that one specimen was the fourth taken on the first case. Clinical evidence of transmission was manifested in the child to a marked extent in four cases (Table I), although in every case there was a marked diminution in the irritability of the child as well as the mother.

CONCLUSION

We conclude, therefore, from both chemical and clinical evidence that sodium bromide is transmitted through breast milk in sufficient quantity to produce an effect upon the nursling.

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ERYTHEMA ANNULARE RHEUMATICUM

Clinical Significance in Rheumatic States of Childhood

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THE attention of the clinician has always been attracted by the occurrence of cutaneous lesions, namely, purpura and erythema, in rheumatic states of childhood. For the most part, interest has centered in the varied manifestations of the exanthem erythema multiforme, particularly with respect to the annular, circinate, or marginate type. The latter form of eruption is generally referred to as erythema annulare rheumaticum and is of importance in connection with the diagnosis of rheumatic heart disease in children. As early as 1835, Rayer[1] described the lesion and suggested its relationship to rheumatic states. In 1881 Barlow and Warner[2] and again, shortly after, Barlow[3] observed that the eruption was frequently present in children with rheumatism and occasionally chorea. In 1889 Cheadle[4] discussed the exanthem in his monograph and stated that the marginate type of erythema which occurred in rheumatic fever was "not infrequently associated with endocarditis and pericarditis in the more serious cases." Thereafter brief references to the lesion were made in the literature. Cockayne[5] noted its association with rheumatism in childhood and described the various ring forms ranging from the more common annular morphology to that of the less frequent erythema iris and herpes iris. Poynton and Paine[6] then indicated that the cutaneous manifestations may occur before the appearance of the complete picture of rheumatic disease or as an isolated instance between recurrent attacks. In 1922 Lehndorff and Leiner[7] directed renewed attention to the significance of erythema annulare rheumaticum and stressed that the eruption is typical and affords conclusive evidence of the existence of organic heart disease of rheumatic origin.

In their description, Lehndorff and Leiner stated that the lesion occurs in children up to 14 years of age, but not among infants of the suckling period. The observers were of the opinion that erythema annulare rheumaticum occurs late in the course of rheumatic infection, not at the outset, and frequently is first noted in children already afebrile and exhibiting manifest signs of rheumatic endocarditis. It is also seen in association with chorea, but never in cases of malignant endocarditis or in endocarditis due to such conditions as gonorrhea, syphilis, or scarlet fever. The early lesions are described as being small, discrete, pink or blue rings, so pale as to be easily overlooked. They are macular,

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never papular, and usually appear on the trunk between the lower half of the chest and the upper half of the abdomen, as well as on the lateral thorax and the back. Less often the lesions are found on the extremities, favoring the inner surfaces of the thighs; the face and mucous membranes are never involved. Itching is absent and hemorrhage, edema, pigmentation, and scaling are not accompanying features. In the more severe form, the lesions grow in size and may become confluent. The duration of the eruption is very variable and may last but few hours or as long as several days.

The conclusions of Lehndorff and Leiner have been accepted by von Leichtentritt,[8] Abt,[9] Perry,[10] and others. The consensus of opinion is that the onset of the eruption is not simultaneous with the occurrence of joint symptoms, but that it becomes manifest after defervescence and when cardiac involvement is evident. It is also stated that the general characteristics of erythema annulare rheumaticum do not run parallel to the clinical severity of rheumatic infection. However, in agreement with the impressions of Poynton and Paine[6] and of Perry,[10] our observations have indicated that the above sequence of events does not always hold true. It is also our impression that at times the severity of the lesion and of the rheumatic infection may be of comparable intensity. We wish, therefore, to present two instances of erythema annulare rheumaticum illustrating these points. In Case 1 the eruption and arthritic symptoms occurred concomitantly, and signs of cardiac damage appeared subsequently. In addition, the severity of the rheumatism and the extent and duration of the eruption ran parallel courses. In the other, Case 2, the rash appeared before the signs of heart involvement, and joint manifestations were evidenced last. Fulminating pneumonia characterized the fatal termination of both cases in which the rheumatic infection represented initial attacks.

CASE REPORTS

CASE 1.—J. K., a 3-year-old white male, was admitted to the hospital with a history of difficulty in standing and fever of two days' duration. This was the boy's fifth admission, having previously been observed for acute laryngitis, hypochromic anemia, and upper respiratory infections. The past history and the family history were otherwise negative.

The present illness began suddenly two days prior to admission when the child complained of inability to stand. At the outset there were no joint pains, and the temperature was 101° F. But several hours later, both knees became swollen and tender, and motion became limited and painful. Two days later the temperature rose to 104° F., and a rash was noted in the right axilla. On admission, physical examination revealed an acutely ill boy in pain. He was dyspneic but not cyanotic. The temperature was 103° F., the pulse rate 128, and respiration rate 34. An irregular macular eruption was present in the right axilla, over both buttocks, and the thighs. The lesions were erythematous and annular with central areas of lighter hue. Herpes simplex was present at the angle of the mouth; the tonsils were enlarged and congested; and there was a marked postnasal discharge. General lymphadenopathy was noted. The lungs were clear. The heart was not enlarged and

the point of maximal cardiac impulse was in the fifth left interspace medial to the midclavicular line. The heart rate was 156 per minute. The sounds were of fair quality and the second pulmonic sound was not unduly accentuated. No murmurs were heard. The blood pressure was 90/46. The liver edge was palpable below the costal margin, but not the spleen. Laboratory tests yielded the following data: the urine was negative; the blood revealed a hemoglobin of 70 per cent (Sahli) and a red cell count of 3,550,000 per cubic millimeter. The white cells were 15,450 per cubic millimeter of which 58 per cent were polymorphonuclear neutrophiles with two staff forms. The sedimentation rate of the blood was 46 mm. in forty-five minutes. The Wassermann reaction was negative, as were the Schick and tuberculin tests. A throat culture showed the presence of *Streptococcus viridans* and *Staphylococcus albus*. The blood culture was negative.

Clinical Course.—On the day following admission, the annular eruption on the buttocks and thighs and in the axilla became more apparent. The lesions varied in size from 2 mm. to several centimeters in diameter; some areas were confluent. As the lesions grew, the centers became paler, and considerable contrast developed with the peripheries. Both knees were swollen and exceedingly painful. On the sixth day of illness the skin eruption had spread over the trunk and lower extremities (Fig. 1). The heart rate remained rapid, but the character and quality of the sounds

Fig. 1.—Case 1. Erythema annulare rheumaticum. Note the extent and distribution of the eruption and the discrete and confluent ring forms.

had not changed. On the seventh day a short soft systolic murmur was first noted in the fourth left interspace near the sternum. One day later the first mitral sound was replaced almost entirely by a blowing systolic murmur. The second mitral sound was loud and sharp and the second pulmonic sound accentuated. The sedimentation rate of the blood was then 70 mm. in forty-five minutes. On the tenth day of illness, the apical systolic murmur became high pitched and musical and the second sound dull and muffled. Roentgenographic examination of the heart showed an accentuation of the right and left borders and a contour indicating mitral valvular disease. An esophagogram showed a marked enlargement of the left auricle. The P-R interval of an electrocardiographic tracing was 0.20 sec. On the thirteenth day of illness the rash disappeared almost entirely. The subsequent clinical course was marked by rapidly progressive rheumatic heart disease. The heart increased in size considerably until the time of death of the boy. Clinically and roentgenologically evidence of pericardial effusion was present. On the day before death the child suddenly experienced marked respiratory distress and a pneumonic infiltration of the right upper lobe was found. During the course of the next twenty-four hours, the pulmonary consolidation spread to both sides and the child died in the seventh week of illness.

Post-Mortem Examination.—Necropsy by Dr. A Plaut showed the following.—*Heart:* About 200 c.c. of clear yellow fluid were present in the pericardial sac. The

heart weighed 165 gm. and measured 8.5 cm. by 8.0 cm. by 6.0 cm. The tissues were soft and edematous throughout. The pericardial surface was hyperemic and exhibited many small and large hemorrhages, particularly over the right ventricle anteriorly where a thick bloody adhesion was seen. The outer surface of the aorta was similarly involved. All cavities of the heart contained large amounts of cruor. The pulmonary cusps were thickened. The endocardium of the right auricle was free of lesions. The left ventricle was enlarged and its endocardium diffusely thickened. Small, partly confluent hemorrhages occupied the base of the right aortic cusp. The aortic cusps also showed irregular thickenings but no definite verrucosities. The mitral valve and the endocardium of the left auricle likewise displayed many confluent irregular thickenings. The myocardium throughout was edematous. Microscopically, although no fully formed Aschoff bodies were seen, the heart showed partly diffuse and partly focal lesions characteristic of rheumatic inflammation. Little was found in the ascending aorta, but the pulmonary artery was the seat of severe rheumatic infiltration. A similar picture was evidenced in the pericardial tissues. Fatty changes were present throughout the myocardium.

Lungs: The pleural surfaces of both lungs showed many large, smooth, depressed cyanotic areas, alternating with smaller protruding pink portions. The right lung was adherent to the pleura at its upper lobe. The cut surfaces were homogeneously red. No focal lesions were found. The bronchi were intensely hyperemic. The lymph nodes were unusually large and soft and their cut surfaces smooth and glistening. Microscopically, the lungs showed hemorrhage, edema, and overgrowth of the capillary endothelium. The capillaries were distended with pale staining red cells. The alveoli contained large numbers of characteristic large mononuclear cells and some smaller cells with deeper staining nuclei.

Anatomic Diagnosis.—Severe rheumatic pancarditis; edema and hemorrhage in the lungs and hyperplasia of the lymphatic apparatus.

Summary.—This case illustrates a first attack of severe rheumatic infection in a three-year-old boy in which joint symptoms and erythema annulare rheumaticum characterized the onset of the disease. The exanthem was extensive, lasting about two weeks and reflecting the intensity of the rheumatic infection. Signs of cardiac involvement, as evidenced by the appearance of a murmur, were first noted on the seventh day of illness. The fatal termination of the case was characterized by severe and rapidly spreading pneumonic infiltration of the lungs. Post-mortem examination showed diffuse rheumatic pancarditis.

CASE 2.—M. B., 8-year-old white female, was admitted to the pediatric service complaining of fever and loss of appetite of two weeks' duration. The family history was irrelevant. The past history was of note in that one year prior to admission the girl had been hospitalized elsewhere for a purpuric eruption associated with bleeding from the gums and nose. A diagnosis of "thrombocytopenic purpura" was made. The clinical course was complicated by intercurrent attacks of varicella and of measles. Tonsillectomy and adenoidotomy were performed at three and one-half years of age. Upper respiratory infections were frequent.

The present illness began acutely two weeks prior to admission, being ushered in by malaise, nausea, vomiting, and fever ranging from 101 to 102° F. Eleven days after the onset of illness the child was brought to the outpatient department because of a rash on the legs and the back. Examination disclosed an annular erythematous eruption. The pharynx was congested and the spleen palpable. No evidence of cardiac involvement was noted. On the following day, the girl's temperature rose to

105° F., and headache appeared. On admission to the hospital, physical examination revealed a well-developed and well-nourished white female who did not appear to be very ill. There was no cyanosis or dyspnea. The skin of the left lower abdomen and of the buttocks showed erythematous lesions of annular morphology, about 1.5 cm. in diameter. The central areas were pale. There were no purpuric eruptions or subcutaneous nodules, nor was there any general or regional adenopathy. The lungs were clear. The heart showed the apical impulse in the fourth left interspace in the midclavicular line. The boundaries of the heart were normal to percussion and the sounds of good quality. Sinus tachycardia with a rate of 138 was present. At this time, two weeks after the onset of illness, a short, soft, localized systolic murmur was first heard at the mitral area. The second pulmonic sound was not accentuated. The pulses were equal, regular, and of good volume. The blood pressure was 88/46. The abdomen was soft, and no viscera were palpable. The deep and superficial reflexes were normal. There was no joint involvement. Laboratory tests showed the following: the urine was negative, but gave a four-plus acetone reaction; the blood showed 5,050,000 red cells per cubic millimeter and a hemoglobin of 88 per cent (Sahli). The white cells were 20,300 per cubic millimeter, and the differential count revealed 74 per cent polynuclear neutrophiles of which 6 per cent were staff forms. The sedimentation rate was 40 mm. in forty-five minutes. The Wassermann reaction was negative; the Shick test was positive; and the tuberculin reaction doubtful. A throat culture showed the presence of hemolytic streptococci and *Streptococcus viridans*. Blood culture showed no growth.

Clinical Course.—Two days after admission, the temperature rose to 104.6° F., and pain in the left knee joint appeared. On the seventeenth day of illness the left knee and ankle became swollen; motion was limited. The skin eruption was not now visible. Two days later, the murmur at the apex of the heart became more marked, and an acute involvement of the right knee joint with effusion appeared. The child was exceedingly ill, dyspneic, and cyanotic. An area of dullness was found over the right middle lobe. Bronchial breathing was present as well as numerous small moist râles. The heart was exceedingly rapid, and the systolic murmur was obscured. The pneumonic infiltration of the lungs spread rapidly to all lobes. The child's condition became rapidly worse, and death occurred on the twenty-first day of illness. Sputum cultures taken just prior to death showed the presence of pneumococcus Type XX, as well as hemolytic streptococci. Cultures were made of fluid aspirated post mortem from the pericardial and pleural cavities and from the right knee joint, but no growth of microorganisms was obtained.

Post-Mortem Examination.—Examination by Dr. A. Plaut revealed the following.—*Heart:* The heart weighed 565 gm. and measured 9.0 by 9.0 by 10.0 cm. The pericardium was smooth, and the sac contained a large amount of clear fluid. There were many subepicardial hemorrhages. The right auricle was enlarged. The left auricle appeared normal. A few small verrucae were seen on the aortic leaflet of the mitral valve; the chordae tendineae appeared thicker than normal and the webs well preserved. The other leaflet was peculiarly soft, and no definite verrucae were visible; the chordae were friable, and the corresponding papillary muscle unusually soft and yellow. The endocardium of the left auricle showed irregular, protruding, yellowish netlike markings. The myocardium was softer and thicker than normal and of yellowish hue. Microscopically, the endocardium of the left auricle was densely infiltrated with leucocytes and mononuclear elements in parallel rows. Many small necrotic areas were present. In addition, large cells with basophilic protoplasm were seen arranged in indistinct ovoid foci resembling Aschoff bodies. As is usually seen in rheumatic lesions, the connective tissue was homogeneous and structureless. Numbers of basophilic, medium sized, round and ovoid cells surrounded small blood vessels in the inner myocardial layers. Throughout the myocardium there were in-

flammatory areas containing mononuclear cells and leucocytes. The homogeneous change in the connective tissue was unusually conspicuous. The posterior mitral area showed very severe inflammation with necrosis at the base of the mitral valve, as well as characteristic Aschoff nodules in the superficial layers of the valvular tissue. Similar changes were present in the posterior papillary muscle, the aortic and mitral valves, and in the pulmonary valve. Other sections showed subendocardial hemorrhages. The myocardium also revealed severe fatty changes irregularly infiltrated. Sections from the thoracic and abdominal aorta showed mononuclear inflammatory foci, and the abdominal aorta contained hemorrhages under the adventitia.

Lungs: The pleural surfaces of the lungs were smooth. The cut surfaces were deeply cyanotic and oozed a large amount of frothy fluid. Microscopically considerable edema was present throughout, and many bronchopneumonic foci were present. Mononuclear elements were seen in the connective tissue around the smallest arteries.

Anatomic Diagnosis.—Rheumatic carditis; bronchopneumonia with severe stasis and edema of the lungs; parenchymatous and fatty change in the kidneys and liver.

Summary.—The foregoing case in an 8-year-old child is characterized by the occurrence of erythema annulare rheumaticum as an advance sign of very severe rheumatic infection. The eruption lasting one week, preceded by several days the initial signs of cardiac damage. Polyarticular symptoms appeared subsequently. The infection was fulminating in course and was complicated by severe terminal pneumonia. Necropsy studies revealed pathologic changes in the heart tissue characteristic of rheumatism.

COMMENT

One of the valuable clinical aids in the diagnosis of the various acute systemic diseases of childhood is the morphologic expression of associated cutaneous lesions. Among the great variety of these eruptions, probably the most commonly encountered in many unrelated disorders are the varied and bizarre configurations of the broad group, descriptively designated as erythema multiforme. From this nonspecific group of eruptions one form, namely, erythema annulare rheumaticum, has been set apart because of its characteristic features and because of its frequent association with rheumatism of childhood.

It is generally agreed by clinical observers that erythema annulare rheumaticum is a specific exanthem of significant value in the diagnosis of rheumatic states of childhood and that it is occasionally evidenced in the allied disorder, chorea. In its occurrence erythema annulare rheumaticum is also stated to appear typically either during the subsidence of rheumatic infection or between recurrent attacks of the disease. The opinion is likewise held that the general clinical characteristics of the eruption do not reflect the degree of severity of the rheumatic process and that its use as an index of prognosis is of questionable value.

However, it seems that the early observations of Poynton and Paine[6] have not been sufficiently stressed. These clinicians emphasized that the cutaneous manifestations may occur before the full picture of

rheumatic infection develops. This observation is brought out by the cases cited above in which erythema annulare rheumaticum appeared as an advance sign of rheumatic disease concurrently with, or preceding, heart and joint involvement. In addition, the extent and duration of the cutaneous lesions in one case ran parallel in its clinical course to the severity of the rheumatism. In its duration, the eruption in the other case likewise appeared to indicate a fulminating clinical course. From the above observations, it seems then that at times the severity of erythema annulare rheumaticum may bear a close relationship to the final outcome of cases of rheumatic disease in childhood. Likewise, the clinical characteristics of the eruption may also indicate an unfavorable prognosis in the disease.

As a final note, it should be borne in mind that, although erythema annulare rheumaticum should strongly suggest existing or impending rheumatic infection, as an isolated sign its occurrence is not always pathognomonic of the disease. Annulare eruptions of erythematous nature may also occur in such conditions as Still's disease[11] and serum sickness.[10]

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Critical Review

CONGENITAL SYPHILIS

Part II. Prevention and Treatment*

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Prevention

CONGENITAL syphilis can be prevented by the adequate treatment of every syphilitic woman during each pregnancy. The first step in prevention is, therefore, the detection of every case of syphilis in women either before conception or soon after conception.

DIAGNOSIS OF SYPHILIS DURING PREGNANCY

Syphilitic infection is frequently masked by pregnancy so that it is often difficult to make a diagnosis of the infection in the ante-partum patient.[67] The diagnosis may be made (1) by the medical history of the patient, (2) by physical examination, and (3) by serologic examination of the blood.

History.—A history of infection with syphilis is often difficult to obtain. Ingraham[44] found that when a "woman was questioned alone, carefully and confidentially, with the thought of syphilis uppermost in mind," a "positive" history was obtained in 80 per cent of the cases at the first interview. He found, however, that without the constant awareness of syphilis and a sympathetic approach on the part of the physician the information was not obtained in half the cases. Dodds[28] obtained a history of syphilis in 64 per cent of a group of 73 cases showing a strongly positive Wassermann reaction. Boas, Gammeltoft, and Sieck[12] obtained a history of infection in 57 per cent of their cases, but Browne[15] was able to elicit a suggestive history in only 25 per cent of his cases. Previous obstetric history is of value, as shown by the fact that 40 to 80 per cent of multiparous syphilitic women give a history of pregnancies resulting in stillbirth, in births of infants who die in early infancy, or in births of syphilitic children.[6, 8, 40, 41, 80, 101] Belding and Hunter[9] were able to obtain histories suggestive of syphilis in 83 per cent of their patients. In 53 per cent of them the history given by the patient indicated syphilis, in 10 per cent the history of previous pregnancies led to a suspicion of syphilis, and in 20 per cent the husband's history was suggestive of syphilis.

Physical Examination.—The clinical signs and symptoms of syphilis are often absent during pregnancy. Welz and Van Nest[107] found during careful examination that among 147 pregnant women who were proved to be syphilitic 20 per cent had syphilitic skin lesions, 29 per cent absent or sluggish reflexes, 12 per cent Argyll-Robertson pupils, and 50 per cent

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a generalized adenopathy. Ingraham[44] found that 24 per cent of 239 syphilitic pregnant women showed syphilis on physical examination.

Serologic Examination of the Blood.—Since in many women the most searching physical examination fails to reveal any evidence of the existence of syphilitic infection, the best, and in many cases the only way to recognize its presence is by means of the routine use of the blood Wassermann test. Occasionally the Wassermann test is negative in a pregnant woman who is later found to be syphilitic. In such a case, in the absence of physical signs, it is manifestly impossible to make a diagnosis during pregnancy except on the basis of the history.[67] The routine use of the Wassermann test in *all* pregnant women, however, will detect the majority of cases of unsuspected syphilis.[110] For example, the reported incidence of syphilis was 5 per cent in 25 prenatal clinics in Philadelphia making routine serologic tests but only 1 per cent in 11 prenatal clinics employing the test merely "as indicated."[45]

In a study reported in 1936, the American Social Hygiene Association found that in 250 of 268 ante-partum clinics the Wassermann test was used routinely, in contrast to its use in only 15 of 37 clinics surveyed in 1925.[33] A study made in 1935 by the same group showed that only half of 82 practitioners made routine Wassermann tests of the blood of their private obstetric patients.[33]

Moore[67] states that pregnancy is *not* a frequent cause of false positive Wassermann reactions. The current consensus on this point is that although nonspecific positive reactions do not occur during the early months of pregnancy, they may appear very rarely in the later months of pregnancy.

FACTORS WHICH INFLUENCE THE FUTURE HEALTH OF THE CHILD OF A SYPHILITIC MOTHER

Factors which influence the health of a child of a syphilitic mother are those chiefly concerned with the therapy administered to the mother and with the stage and activity of the infectious process in the mother.

Therapeutic Factors.—Treatment given a syphilitic woman during pregnancy is directed primarily toward preventing or curing syphilis in the infant and only secondarily toward curing the mother. The therapeutic factors of importance from the point of view of the infant are (a) the amount and kind of therapy received by the mother during pregnancy, (b) the time during pregnancy when therapy was received, and (c) the amount of therapy received by the mother before conception.

A. Treatment During Pregnancy.—It is generally conceded that an arsenical should be used in treating the pregnant syphilitic woman. Bismuth or mercury is almost routinely used with the arsenical. The arsenicals which have been most commonly used with the best results are arsphenamine and neoarsphenamine. More important than the choice of arsenical is the amount of drug administered during pregnancy. There appears to be a direct correlation between the amount of drug given and the proportion of healthy children produced in a given number of pregnancies. McKelvey and Turner[60] used arsphenamine in the treatment of 382 pregnant syphilitic women. The ultimate clinical status of 271 children of these women was ascertained. When the mother had received prenatally less than 1 gram of the drug, 73 per cent of the children were nonsyphilitic; 1 to 2 grams, 80 per cent; 2 to 3 grams, 84 per cent; 3 to 4 grams, 88 per cent; and 4 to 6 grams, 100 per cent. Ingraham[44] also

used arsphenamine and reported that among a group of syphilitic women receiving no prenatal treatment 20 per cent had nonsyphilitic children, those receiving less than 4 injections, 29 per cent; 4 to 8 injections, 52 per cent; 9 to 16 injections, 61 per cent; and more than 16 injections, 85 per cent.

Acetarsone or acetylarsan has been used in the treatment of syphilis in pregnant women, but reports of the results are not conclusive. Castallo and Rakoff,[19] for example, used acetylarsan in the treatment of 57 syphilitic pregnant women, 97 per cent of whose pregnancies resulted in live births. They compare these results with those of a similar series in which they used arsphenamine and obtained essentially the same results (95 per cent live births). Coppolino,[25] however, found the results with acetylarsan distinctly inferior to those with neoarsphenamine. Thirty-one syphilitic women treated during pregnancy with neoarsphenamine gave birth to 30 normal and only 1 syphilitic infant, while 39 syphilitic women treated with acetylarsan gave birth to 14 normal and 15 syphilitic infants.

Klaften[50, 51] has reported somewhat inconclusively on the use of malaria therapy during pregnancy in syphilitic women.

B. Time of Administering Treatment.—Treatment should be started before the fifth month of pregnancy if the largest number of fetuses are to be saved, since infection of the fetus probably takes place after the fourth month of gestation. The Cooperative Clinical Group[22] found that when treatment was started between the first and fifth months 22 per cent of the pregnancies of syphilitic women ended "disastrously" for the fetuses; when treatment was started between the fifth and tenth months 39 per cent ended "disastrously." McKelvey and Turner[60] found that the incidence of fetal and neonatal deaths was lowest when syphilitic women were given arsenicals during the last trimester of pregnancy, regardless of the amount of treatment previously received by them.

Treatment during the early months of pregnancy does not cure the mother of her infection, but the treatment protects the fetus from infection. If the concentration of the drug in the mother's tissues is not maintained throughout pregnancy, periodic invasion of the blood stream by spirochetes may occur resulting in infection of the fetus.

A questionnaire survey made by a committee of the Medical Women's National Association, aided by the American Social Hygiene Association, showed that, in 9 clinics serving 3,400 patients during 1923, 76 per cent of the pregnant women were first seen during the first six months of pregnancy.[75] In a similar but much larger series of cases studied by Exner[33] in 1935, it was found that conditions with respect to early attendance at ante-partum clinics had not changed materially. Of 142 clinics reporting, 62 stated that 50 per cent of their patients were seen before the middle of pregnancy. A survey[103] in the spring and summer of 1937 in Chicago indicated that in less than half the syphilitic pregnant women had the disease been detected before the fifth month of pregnancy, and among these women only 21 per cent had received adequate treatment.

C. Anteconceptional Treatment.—The question whether or not women who have once had syphilis should be treated in every subsequent pregnancy has been raised again recently by several workers. Reports made by McKelvey and Turner[60] and by the Cooperative Clinical Group[22] in-

dicate that treatment received prior to pregnancy will be of definite advantage in a future pregnancy but that such treatment will not insure the birth of a healthy infant as often as does treatment during pregnancy. Birnbaum[10] reported the cases of 21 women with early syphilis who were given rigorous antisyphilitic treatment "to the point of complete cure." The author studied the 34 subsequent pregnancies of these women; none of them was treated during pregnancy, and all of the children were apparently healthy. Some of them have been examined as late as six years after birth. Ingraham and Kahler[45] contend that in the light of our present knowledge of the curability of syphilis the obstetrician takes an unwarranted risk in permitting such women to go through pregnancy without antisyphilitic treatment. The Cooperative Clinical Group (1938)[69] recommends that the syphilitic mother be given "early and adequate treatment throughout every pregnancy."

MATERNAL FACTORS INFLUENCING THE OUTCOME OF PREGNANCY IN SYPHILITIC WOMEN

The Cooperative Clinical Group studied the mother's serology before and during pregnancy in relation to the result of pregnancy. They found that 39 per cent of pregnancies ended disastrously for the infant among women whose Wassermann reactions were positive before and negative during pregnancy compared with 43 per cent when the Wassermann reactions remained positive during pregnancy. The results of the pregnancies were studied in relation to the stage of the maternal infection. It was found that the stage of the infection was apparently not a definite factor in the transmission of the infection to the child as long as the Wassermann reaction remained negative during pregnancy. When the Wassermann reaction was positive during pregnancy, however, those women with active syphilis transmitted the disease to their infants in 31 per cent of the cases, whereas those women with positive serology but a latent infection transmitted the disease to the offspring in only 19 per cent of the cases.[22]

Fordyce and Rosen[36] recommended in 1922 that all pregnant women be treated for syphilis on the mere suspicion of the presence of the disease. Barnett[4] treats a pregnant woman for syphilis when the only indication is the presence of the disease in the husband. Many workers (Barnett,[4] Macnicol,[61] Abraham,[2] and Spiegler[91]) recommend that women receive antisyphilitic treatment during every pregnancy if they have been known to have had the disease, regardless of the amount of therapy received and regardless of the Wassermann reaction.

Since reactions of the mothers to antisyphilitic therapy have been used as an argument against treating the syphilitic woman during pregnancy, the Cooperative Clinical Group[22] studied the toxic reactions to antisyphilitic treatment during pregnancy and concluded that arsenical treatment need never be withheld from a pregnant woman for fear of irritating the kidneys or causing arsenical reactions. Ingraham and Kahler,[45] on the other hand, found that the only death from arsphenamine occurring in the University of Pennsylvania Hospital in a series of 17,000 injections was in a pregnant woman. Kristjansen[54] reports a few serious reactions in pregnant women. However, there is almost universal agreement that the pregnancy is not a contraindication for vigorous antisyphilitic treatment.

Treatment of Congenital Syphilis in Early Infancy

It has been said that the best means of treating congenital syphilis is to prevent it. The methods of prevention are well known, but the fact that in this country 60,000 infants[76] each year are born with congenital syphilis shows that all syphilitic women do not receive adequate treatment during pregnancy. The problem of treating the infected newborn infant remains, therefore, an important part of the attack upon syphilis.

THE PROBLEM OF THE SELECTION OF INFANTS FOR THE ADMINISTRATION OF ANTISYPHILITIC TREATMENT

Infants of untreated or inadequately treated syphilitic mothers may or may not be infected. There is no problem in deciding whether to administer antisyphilitic treatment when infants show manifestations of syphilis at birth; but many syphilitic infants show no signs of the disease at birth,[3, 21, 46, 96] and it is difficult to decide whether or not to treat these infants. There are two main groups of authorities who hold different opinions on this matter. One group[3, 63, 65, 78, 85, 92, 98] advocates the treatment of all infants of syphilitic mothers, whether clinical signs of syphilis are present or absent in the infant. Another group[1, 11, 16, 25, 45, 67] advocates that no infant should be treated for syphilis until the diagnosis is established. The literature has been searched for evidences of the advantages of giving or withholding treatment of apparently healthy infants of syphilitic mothers, and the information has been briefly summarized as follows:

The reasons that have been advanced for treating all infants born of syphilitic mothers are:

1. It is often impossible to tell at birth which infants are infected with syphilis and which are not.
2. Treatment of the mother results in treatment of the fetus in utero, and the infant at birth, although infected, may show no evidence of the disease. The treatment of the infant should not be interrupted at birth.
   In cases in which the mother is treated throughout pregnancy, a course of treatment given to the infant postnatally may be necessary to supplement his prenatal treatment. (It is assumed that the infant's tissues are permeated by these drugs given to the mother.)
3. The incidence of late complications of syphilis in the infants of syphilitic women is decreased.
4. If a syphilitic infant, apparently healthy at birth, is not treated immediately after birth an unjustifiable risk is taken in that the disease may not be detected early and therefore treatment may be necessarily delayed.

The reasons that have been advanced for withholding treatment until a definite diagnosis of congenital syphilis in the infant has been established are:

1. If treatment for syphilis is begun it should be continued for a long period. (It is here assumed that the fetus does not receive antisyphilitic treatment administered to the mother.)

2. It is impossible to evaluate the results of therapy unless the diagnosis is established in each instance.
3. It is not justifiable to place the stigma of syphilis on a nonsyphilitic child.
4. It is a needless risk to submit a nonsyphilitic infant to the hazards of antisyphilitic therapy.
5. It is an unjustifiable expense to treat nonsyphilitic infants.

These differences of opinion are based upon differences in interpretation of the mechanism of prenatal treatment of the mother.

Almost all authorities agree that infection of the fetus does not take place before the fourth to fifth month of pregnancy.[38, 46, 52, 67, 77, 86] Therefore treatment of the mother started at this time or earlier probably prevents the infection in the fetus either by sterilizing the maternal blood stream or by preventing transfer of the organisms to the fetus by concentration of antispirocheticidal drugs in the placenta.[46, 67] There is agreement also that to prevent infection of the fetus it is necessary to continue treatment of the mother with arsenicals during the last months of pregnancy in order to insure a maintenance of the concentration of the drug in the maternal blood, in the placenta, or in both.[30, 82, 102]

Treatment of the mother begun even late in pregnancy materially reduces the incidence of infection of the offspring.[22, 60, 62, 83] It is in regard to the mechanism by which treatment of the mother begun late in pregnancy affects the welfare of the fetus that authorities have disagreed.

One group believes that the drugs used in the treatment of the mother late in pregnancy actually saturate the tissues of the fetus, which is already infected. The permeability of the placenta to the drug is said to be proved by the concentration of antisyphilitic drugs found in fetal tissues. Eastman and Dippel[31] found large amounts of arsenic in the meconium of infants born of mothers who received arsphenamine during pregnancy. Levy and Selter[58] detected bismuth in both placenta and fetuses of rabbits. Kraul and Bodnar[53] found bismuth in the human amniotic fluid after therapeutic doses had been given to the mother, and Caffey[17] detected bismuth in the bones of infants whose mothers received bismuth during pregnancy.

Another group considers that treatment of the mother late in pregnancy prevents infection of the fetus by concentration of the antisyphilitic drugs in the placenta or by a continuous sterilization of the maternal blood stream. The mechanism is exactly the same as that of treatment early in pregnancy. This group maintains that the placenta is relatively impermeable to antisyphilitic drugs administered to the mother. Voegtlin[106] and others found less arsenic in the embryo than in any maternal tissue. Vamos and Böhm[104] were unable to detect arsenic in the fetal organs of rabbits whose mothers had been given intravenous arsphenamine. Leonard and Love[57] could detect only very small amounts of bismuth in fetal tissue.

If the theory of the first group is accepted, that is, the infected fetus is treated in utero, there would seem to be a rational basis for treating all infants of syphilitic mothers; if the theory of the second group is accepted, that is, that treatment of the mother prevents infection of the fetus, these infants need not be treated until a diagnosis can be established.

Klaften[50] states that if the offspring of untreated syphilitic women are permitted to go without specific treatment for syphilis until they are clinically syphilitic, 56 per cent will die in the first three months of life, whereas if all are treated immediately after birth the mortality rate will be only 16 per cent.

Morgan[70] states that more than 90 per cent of the deaths from this disease occur in the first few months of life, and he concludes from his own research that 80 per cent of syphilitic infants can be serologically cured if treatment is instituted at birth. Sylvester[96] says: "My conviction is that the baby who is seen early and treated adequately and early, will become normal in every way and remain so for so long that it may be considered cured."

It has been found, moreover, that from 70 to 80 per cent of infants born of mothers who have received only one month or less of prenatal treatment, or of mothers whose syphilitic infection is recent and active, will develop congenital syphilis.[44]

THE PROBLEM OF TREATING SYPHILITIC INFANTS

The treatment of congenital syphilis in early infancy is complicated by the fact that the disease in its active form frequently produces a severe toxemia and that severe constitutional disturbances may result.[67] The aim of treatment is therefore twofold: to preserve the life of the infant and to cure the infection.

General pediatric care is of great importance in preserving the life of the congenitally syphilitic infant. Breast feeding is recommended by Stokes,[93] but he warns against permitting any one but the mother to nurse a syphilitic infant, whether the infant has obvious signs of syphilis or not, because of the possible danger of infecting a healthy woman. The mother should be under treatment during the period of lactation, and the infant will receive some benefits from antisyphilitic drugs transmitted through the milk. Most investigators think that such medication is of minor significance in treating the infant. Campbell and Frost,[18] however, recommend treatment of the infant by means of the mother's milk as the sole specific treatment in certain cases.

Syphilitic infants should be protected from respiratory and intestinal infection, since their ability to resist infection is decreased.

Mortality of congenitally syphilitic infants in the first few months of life, whether they are treated or not, is high. Sylvester[97] found that during the twenty-five years' period, 1901-1925, nearly all of a series of infants who showed definite clinical signs of syphilis within the first three weeks of life died. He noted no decrease in mortality for this age group during the decade, 1915-1924, when methods of general care and treatment of syphilis had greatly improved. Jones[47] found 100 per cent mortality among syphilitic infants who showed manifest lesions during the first month of life, a 17 per cent mortality among infants who did not develop signs of syphilis until the second to the sixth month, and an 8 per cent mortality among those who did not develop signs of syphilis until the second half of the first year. Smith,[89] in making a study of the records of 621 syphilitic infants, found that 91 per cent of the deaths directly attributable to syphilis occurred in infants under six months of age.

The severity of the lesions was found by Jones[47] to influence mortality. Severe syphilis was found in 34 per cent and mild lesions in 5 per cent of the children dying in the first year.

The amount of treatment was found by Smith[88] to influence mortality. Twenty-two per cent of the infants dying of syphilis had received no treatment, 12 per cent had received less than six injections, and 2 per cent had received more than six injections.

Many congenitally syphilitic infants die of causes not directly associated with syphilis. Respiratory diseases take a heavy toll during the first year. Fürst[37] found that of 702 congenitally syphilitic children more than half died, approximately one-third of the deaths being due to pneumonia.

TECHNIQUE OF THERAPY

1. *Drugs Used.*—The antisyphilitic drugs that have been used in the treatment of congenital syphilis and the usual routes of administration are as follows:

Arsenicals	
Arsphenamine	intravenous
Neoarsphenamine	intravenous (occasionally intramuscular or, rarely, intraperitoneal)
Sulfarsphenamine	intramuscular and subcutaneous
Mapharsen	intravenous
Acetarsone	oral
Heavy Metals	
Bismuth	intramuscular
Mercury	inunction, oral, or intramuscular
Combination of Arsenical and Heavy Metal	
Bismarsen	intramuscular

2. *Routes of Administration.*—In pediatric practice the routes of administration of the antisyphilitic drugs and in some cases the ease of administration, rather than the efficacy of the drug, have often determined the type of therapy.

The technique of intravenous administration is difficult to use in young infants because of the small size of the veins and the lack of cooperation on the part of the patient. The cubital or jugular veins are commonly employed. Moore[67] warns especially against the use of the longitudinal sinus by way of the anterior fontanel because of the danger of infiltration of the brain substance.

Intramuscular injection is not a difficult technique for the physician, but it is sometimes painful for the patient, and some physicians feel that the obvious discomfort caused by such treatment interferes with the regularity with which mothers are willing to bring their infants to the clinic.

The oral route is free from all the difficulties and discomforts of any treatment "by needle." It is, however, a somewhat unreliable method of treatment, since the physician can never be sure how much of the prescribed drug is actually taken by the patient when the entire responsibility for its administration is left in the hands of the mother.

Intraperitoneal injection of neoarsphenamine has been advocated by Grulee, Sanford, and Waldo[39a] in cases in which rapidity of action is desired and the small veins make intravenous injection impossible. In a personal communication to the authors Sanford states that intraperitoneal therapy is now used only as "an emergency measure in florid cases to achieve rapid action."

3. *Intervals of Treatment.*—The treatments are usually given at weekly intervals. There are three different methods for giving courses of treatment. In the first, called continuous therapy, courses of arsenical and heavy metal follow each other without rest periods. In the second, intermittent therapy, courses of treatment are separated by intervals of varying lengths of time. In the third, intensive treatment, large doses of arsenical and heavy metal are given in a short period of time, followed by a comparatively long rest interval before the next phase of the treatment begins.

The Cooperative Clinical Group[95] has demonstrated that for adults continuous therapy is considerably superior to intermittent, irregular, or intensive treatment. Their findings are in accord with the theoretical explanation set forth by Moore and Keidel[68] in 1926 when they introduced into the Johns Hopkins Clinic the continuous treatment in which alternating courses of arsphenamine and heavy metal are given. No similar studies have been made for children. The results of the intensive method used in treating children have been reported by McBride,[59] by Schussler,[87] and by Kundratitz.[56] McBride's intensive treatment consisted of three injections of arsphenamine at forty-eight-hour intervals and in addition an injection of bismuth at the time of the first and third arsphenamine injections, followed by six weeks of treatment with mercury and chalk by mouth. The entire course was then repeated. Schussler's intensive course consisted of 8 doses of neoarsphenamine in three weeks, followed by 16 mercury inunctions in eight weeks and then a two-week rest period. Four such courses were given in the first year. Kundratitz has also reported the results of intensive treatment of infants.

These investigators might be considered to have used massive rather than intensive treatment in the sense used by Moore,[67] as no long rest periods without treatment were allowed between courses. The results obtained by them are shown below. It should be pointed out that the term "cured," as used by these authors, means freedom from clinical and serologic signs of syphilis for periods varying from a few months to two years.

AUTHOR	TOTAL CASES ADEQUATELY TREATED	PER CENT "CURED"
Schussler	13	100.0
McBride	19	100.0
Kundratitz	58	89.6

THE ARSENICALS

1. *The Arsphenamines.*—The general principle followed until recently in treating infants with congenital syphilis has been to use the same drugs used in treating adults and to make the dosage proportional to the weight of the infant. As knowledge of chemotherapy has advanced, however, it has been found that certain drugs are more suitable than others for treating infants.

Prior to 1922 almost all infants treated for congenital syphilis received either arsphenamine or neoarsphenamine. White and Veeder[108] were able to follow 22 infants who received an adequate amount of arsphenamine and mercury and found that only 59 per cent had been clinically and serologically cured. Morgan[70] found that 80 per cent of 75 syphilitic

infants who were adequately treated with arsphenamine and bismuth and whose cases were followed for at least two years remained clinically and serologically free from syphilis. Smith[88] reported very similar results: 78 per cent cures among 49 children adequately treated with arsphenamine and bismuth.

Meyer[66] reported the results of the use of neoarsphenamine in the treatment of 127 syphilitic infants, 97 per cent of whom became serologically free from syphilis and continued free when examined from one to two years after the cessation of treatment. Fordyce and Rosen,[36] however, obtained only 55 per cent serologic and clinical cures after treating 55 syphilitic children with neoarsphenamine and mercury. Wile and Shaw[109] obtained disappearance of symptoms and serologic reversal in 90 per cent of children most of whom were treated with neoarsphenamine. Jones,[47] however, found no manifestations of syphilis in any of 13 infants who were adequately treated with neoarsphenamine and bismuth.

In 1922 Voegtlin, Johnson, and Dyer[105] discovered that sulfarsphenamine had a greater spirocheticidal property than either arsphenamine or neoarsphenamine and that experimental animals tolerated the drug well when it was administered intramuscularly. For the treatment of infants and children the advantages of a drug that could be administered intramuscularly soon became apparent.

Although the use of sulfarsphenamine for the treatment of syphilitic infants has received unqualified endorsement by the Clinical Cooperative group,[69] reports of the results of its use are few in number and not entirely satisfactory. Crawford and Fleming[26] used sulfarsphenamine combined with mercury in the treatment of 23 infants and 12 older children, but they reported that many of their patients remained Wassermann-fast. Boone and Weech[13] treated 21 infants and obtained good immediate results with no serious reactions, but they did not follow their cases long enough to obtain any data on the ultimate effect of the drug. Dunham[29] treated 5 infants and 23 older children with sulfarsphenamine combined with mercury. She concluded that the drug was not superior to neoarsphenamine for the treatment of syphilis but that its greater ease of administration gave it a place of value among the available antisyphilitic drugs. Atlee and Tyson[3] treated 106 infants with sulfarsphenamine combined with bismuth and observed no serious toxic manifestations; 98 of the infants became clinically and serologically free from syphilis and 8 remained serologically positive. It is important to point out, however, that some of the infants treated as syphilitic had as the only evidence of syphilis a positive Wassermann reaction of the cord blood.

Jeans and Cooke[46] and Moore[67] advocate the use of sulfarsphenamine in the treatment of congenital syphilis in early infancy because of its ease of administration and the low incidence of toxic manifestations.

2. *Acetarsone.*—This drug (a pentavalent arsenical) is known as acetarsone in the United States, as stovarsol in France, as spirocid in Germany, and as osarsol in Russia. It was first prepared by Ehrlich and Hata in 1908.

Acetarsone was used very little until about 1921, when a series of reports from France indicated that it was effective in the treatment of syphilis in children when given orally. Since that time there have been many reports, especially from Germany, on the value of acetarsone in

the treatment of congenital syphilis. The drug has come into more or less common use in the United States in the past five years. The fact that acetarsone can be given by mouth, thus avoiding the difficulties of injections, accounts in part for its widespread use.

In spite of the fact that acetarsone has been in use since 1921 and that the literature contains about forty reports dealing with the treatment of more than 1,100 children, only four reports have been found in which sufficient follow-up has been made to evaluate the drug.

The dosage, method of administration, toxic effects, and immediate therapeutic value of acetarsone have received considerable attention. Acetarsone is a white crystalline powder conveniently dispensed in tablets containing 0.10 and 0.25 gram. It must be administered by mouth. The general opinion is that infants and children tolerate this drug best when it is given in small, gradually increasing doses. The size of the daily dose, the length of a course of treatment, and the total amount of drug given in a course have varied widely.

At the present time two plans of treatment are in comparatively frequent use in the United States. The more conservative plan is that devised by Bratusch-Marrain.[14] The dosage is based upon the weight of the child as follows:

First week	0.005 gram per kilogram daily
Second week	0.01 gram per kilogram daily
Third week	0.015 gram per kilogram daily
Next six weeks	0.02 gram per kilogram daily

The amount of acetarsone in grams consumed during one nine-week course by this system corresponds approximately to the weight of the infant in kilograms. For example, an infant weighing 6 kilograms would receive approximately 6 grams of acetarsone during one course of sixty-three days. This course of treatment is followed by a rest period of four to six weeks, and then the course of treatment is repeated until the Wassermann reaction, taken after every course, is negative three times in succession. An additional "safety course," given six months after the cessation of the regular course, is recommended even in the presence of a negative Wassermann reaction.

The plan of Maxwell and Glaser[63] is less conservative than that of Bratusch-Marrain. In this method of treatment the infant receives 14 grams of acetarsone in a forty-nine-day course, approximately twice as much acetarsone as that recommended by Bratusch-Marrain, and it is administered during a shorter period of time.

Both these methods of therapy call for continuous treatment during the course, followed by a six-week rest period between courses. Some German authors have advocated that treatment and rest follow each other at intervals of several days during the entire course of treatment. Baumbach[5] attempted to determine the relative value of these two plans of treatment. Equal doses of acetarsone were given to each of two groups of children, to one group in a six-week course, to the other in a twelve-week course (one week of treatment alternating with one week of rest). The conclusion reached was that the twelve-week intermittent course produced more reversals of the Wassermann reaction than did the six-week course. No further data have been found on this point. In this country almost all investigators administer acetarsone in continuous courses.

The question whether acetarsone is more efficacious when administered alone or combined with a heavy metal has also been commented upon in several reports. Baumbach[5] found that when mercury was given during the rest periods of the intermittent course (one week of acetarsone, one week of mercury) better results were obtained than when acetarsone was given alone. Rambar[80] gave mercury during the six-week rest periods, following the nine-week acetarsone phase of the Bratusch-Marrain plan of treatment. No better results could be detected than when acetarsone was given alone. Von den Steinen[92] and Joseph[48] both recommend bismuth injections alternating with acetarsone in an intermittent course (three days of acetarsone, three days of bismuth). Traisman[100] states that bismuth should be given during the six-week interval between continuous courses, especially to older children.

Reports of the effect of acetarsone on the lesions of syphilis in infants have been almost uniformly favorable. Pillsbury and Perlman[79] observed that spirochetes disappeared in seventy-two hours from lesions in which dark-field examinations were made at twenty-four-hour intervals.

In addition to the specific effect of the treatment, improvement in the general condition of syphilitic infants treated with acetarsone is frequently reported. Nedelmann,[74] Traisman,[99] and Huber[43] reported satisfactory gains in weight for syphilitic infants under treatment with acetarsone. Improvement in color, with a corresponding rise in hemoglobin content of the blood, has been noted.[34, 84, 92] Improved resistance to infection has been reported by Kiss,[49] Krombach,[55] and Menne.[64]

The effect of acetarsone upon the blood Wassermann reaction of infants has been reported to be satisfactory, but the reports are not convincing since many of the infants were not seen after completion of the treatment.

Comparisons of the immediate results of acetarsone therapy with the results of the older methods of treatment have been attempted. Davidson and Birt[27] reported, for example, that 14 of 23 children treated with acetarsone were "cured" in a two-year observation period as compared with only 6 of 27 patients treated with other drugs in a seven-year observation period. Bratusch-Marrain[14] reported that of 23 children under one year of age who were treated with acetarsone 14 were "cured" as compared with 6 of 27 children treated with neoarsphenamine. Pillsbury and Perlman[79] found that cutaneous lesions healed more quickly under acetarsone treatment than under bismuth treatment, but not so quickly as under arsphenamine treatment. Hom[42] states that the external symptoms of syphilis disappear during acetarsone treatment in the same time as under neoarsphenamine treatment, but that the visceral lesions respond more quickly to treatment with mercury, neoarsphenamine, and bismuth.

Toxic effects are produced in certain individuals by acetarsone as by other arsenical drugs. The majority of the reactions are mild, but since the introduction of the drug there have been 7 deaths reported among over 1,000 children which were directly attributable to its use. These deaths were reported to be due to "poisoning" of the central nervous system, "toxic dyspepsia," and "reactions of an exanthem nature." The mild reactions are controlled by discontinuing the drug for a brief time, during which the body eliminates accumulated arsenic after which acetarsone can usually be continued without any further untoward

effects. The reported incidence of toxic reactions has varied. Traisman[100] feels that the size of the dose is directly related to the seriousness of the toxic reactions. He considers the dosage used by Maxwell and Glaser too high for many infants. He also states that rest periods between courses are essential to allow for the elimination of arsenic and to avoid reactions.

Most workers emphasize the fact that patients receiving acetarsone must be under constant medical supervision and should not be allowed to take long courses of the drug without a check-up by the physician, since many serious reactions can be avoided by detecting early signs of toxicity and temporarily discontinuing the drug.

From a review of these reports it is clear that at the present time it is impossible to draw any conclusion as to the optimum dosage and the system of administering acetarsone. Further controlled studies are needed to settle the present uncertainties.*

In a recent review, however, Yampolsky[112] states that he now considers acetarsone the drug of choice in treating congenital syphilis in young infants. Griffith and Mitchell[39] in the recent edition of their textbook report extensive use of acetarsone.

3. *Bismarsen (Bismuth Arsphenamine Sulfonate).*—An advantage of the use of this drug is that the therapeutic effects of arsenic and bismuth are combined in one drug. It was synthesized by Raiziss in 1925 and was first used for the treatment of adults in 1927 by Stokes and Chambers,[94] who reported very satisfactory results. Chambers and Koetter[20] and Reilly[81] used the drug for the treatment of congenital syphilis in children.

Bismarsen is given by the intramuscular route only. Stokes says that it should be used continuously for long periods and that the interval between injections should not be greater than three or four days. Chambers and Koetter gave bismarsen to children twice weekly in twenty injections, with rest intervals of two weeks between the first and second courses and of one month between the second and third courses. Therapeutic effects were good, but healing of lesions was not so rapid as under treatment with arsphenamine derivatives. Wassermann reversal was obtained in 91 of 100 children. Of the 91 children, 41 of whose cases were followed for twenty months, 5 showed "serologic relapse." Reilly gave bismarsen in weekly injections to 170 children; the serologic records of 61 patients were followed, and in 47 cases the reaction became negative. Ten of the 170 children suffered clinical relapses, and 8 suffered a serologic relapse after cessation of the treatment. It is possible that Chambers and Koetter obtained better results than Reilly because they administered the drug twice weekly and Reilly gave it only once a week.

Neither Chambers and Koetter nor Reilly encountered any serious toxic reactions in children in the course of over 9,200 injections. Mild reactions were found in about the same frequency as with the use of the other arsenical compounds. Yampolsky[112] says that in his experience bismarsen causes pain and therefore he has discontinued its use.

*Since this article went to press Dr. Pillsbury and Dr. Perlman, of the University of Pennsylvania, have furnished us with an unpublished manuscript giving the results of treatment with acetarsone of 187 syphilitic infants and children, using the Maxwell-Glaser plan of treatment. Toxic reactions occurred in 11 per cent of the children; in more than one-third of the toxic cases evidences of nephritis were found. In these cases the use of the drug was discontinued. Eighty-seven of the 187 children were observed for three years or more. In none of the cases did a clinical relapse occur; in only one case was there a serologic relapse.

4. *Mapharsen.*—This is the trade name for arsenoxide (meta-amino parahydroxy phenyl arsene oxide). Recent theoretical work lends support to the theory that arsenoxide is the agent in vivo which produces the spirocheticidal effect when the arsphenamines are injected. The suggestion has been made that, if this is true, the beneficial results of arsphenamine would be obtained by using arsenoxide for therapy and many of the complications of arsphenamine therapy would be avoided.

Reports on the use of this drug in infants and children are very few. Morgan[71] treated 39 syphilitic infants and children and kept them under observation for sixteen months. He compares the results of treatment in this series of cases with those of another series of children treated with other drugs during the past nineteen years. In giving 935 injections of mapharsen mild reactions were observed in 133 cases and a moderately severe reaction in 1 case. The dosage used was 0.5 mg. to 0.75 mg. per kilogram of body weight. He concludes that, although a complete evaluation of the drug is not yet possible, the results strongly suggest that mapharsen is a more powerful agent in effecting a serologic cure than any other arsenical compound previously used in his clinic.

Studies of the use of mapharsen are being made in several clinics at the present time.

THE HEAVY METALS

Two heavy metals (mercury and bismuth) are used for the treatment of syphilis in children. Mercury is one of the oldest known antisyphilitic remedies, but bismuth, which has come into use more recently, is rapidly replacing it.

1. *Mercury.*—In 1920 Findlay[35] said that treatment by mercury alone should be discarded. He reported that in a series of infants under three months of age who were treated with mercury alone the mortality was 71 per cent, while in two series of cases in which combined treatment with mercury and an arsenical was used the mortality was 37 and 26 per cent, respectively. There are, however, occasional reports in the recent literature of mercury being used as the sole drug in the treatment of congenital syphilis.

2. *Bismuth.*—Müller[73] reported the use of bismuth in the treatment of syphilis in children in 1922. Since that time there have been numerous reports of the use of bismuth alone or in addition to other therapeutic agents. Bismuth is said to stimulate the resistance of the host to invasion by the spirochete. It has, in addition, some direct antispirocheticidal properties which mercury does not have, although its action in this respect is not so great as that of the arsenicals. Bismuth is less toxic than mercury. Bismuth has been administered by several routes, but Stokes[93] says that the intramuscular route is the only practical one.

There are six preparations of bismuth in relatively common use at the present time and they vary according to the vehicle (water or oil) and the chemical constitution of the drug.

The water-soluble preparations require relatively frequent administration, two to three times per week; the oil-soluble preparations require less frequent administration, usually once a week.

The dosage of bismuth usually follows the Lomholt rule of 0.5 mg. bismuth metal per kilogram of body weight per day. It is usually considered good practice to allow rest periods of six to eight weeks between courses.

The clinical response to bismuth therapy has in general been reported to be satisfactory. Skin and mucous membrane lesions heal rapidly. Wright[111] found that the Wassermann reaction was reversed in some children when this could not be accomplished by other methods of treatment. Coppolino[24] reported good results with the use of bismuth in treating infants but found it less effective in older children. He does not consider it so useful a drug as acetarsone.

Some toxic reactions occur with intramuscular injections. They consist of anorexia, vomiting, and diarrhea with, occasionally, black deposits of bismuth sulphide in the mucous membranes. Occasionally cutaneous symptoms or generalized reactions take place, but they are rare. Beerman[7] studied the cases of fatal poisoning due to bismuth that were reported in the literature up to 1932 and concluded that intravenous administration (purposeful or accidental) was primarily responsible for sudden deaths.

PROGNOSIS

The tendency for syphilis to produce clinical signs or symptoms many years after the initial infection has led many syphilologists to give a very guarded prognosis of complete cure of syphilis even in children. Smith[88] has shown that the longer a group of children were under observation the larger was the number of relapses. In his series of children treated before the age of 2 years, relapses took place in 65 per cent of the cases five to twelve years after the child had been discharged from treatment. When these cases were followed for more than thirteen years after discharge it was found that relapses occurred in an additional 15 per cent of the cases. Smith[88] found that relapses were much more frequent in children whose blood Wassermann reactions remained persistently positive than in those whose Wassermann reactions became negative under treatment. The ultimate effect of treatment was found to depend upon the age at which treatment was begun and upon the amount and type of treatment given.

Smith reported that 9 per cent of children receiving "adequate" treatment suffered relapses, compared with 14 per cent of those receiving "inadequate" treatment. Jones[47] found that all infants were "cured" under "regular" treatment and only 50 per cent under "unsatisfactory" treatment.

Smith[88] found that, when treatment for syphilis was started before the third month of life, the relapse incidence was 6 per cent; between 4 to 6 months, 11 per cent; and between 7 to 12 months, 15 per cent. When treatment was delayed until some time during the second year, the relapse incidence was 19 per cent. White and Veeder[108] found that when treatment was started before the age of 2 months, 32 per cent of the children were "cured," compared with 25 per cent when treatment was started after the second month but before the second year.

The kind of antisyphilitic therapy used must necessarily influence the ultimate clinical outcome. Because of the large number of variables influencing the end results, however, it is not possible to obtain data regarding the most efficacious treatment. The amount and regularity of treatment, the age at which treatment is begun, the severity of the manifestations of syphilis, and the pediatric care of the infants are all perhaps as important as the selection of the drug or drugs used. There is a lack of controlled studies of the effect of different types of treatment.

In thirteen reports[32, 36, 46, 47, 56, 70, 72, 74, 87, 88, 90, 108, 109] of over 2,000

children diagnosed as syphilitic and treated by well-known methods before the age of 2 years, it was found that only one-fourth of the children were adequately treated and followed long enough to determine the results.

Fifty-five to 100 per cent of clinical and serologic cures are recorded in the various reports on this group, but no constant relation appears between the method of treatment and the percentage of cures.

It is impossible, considering all the variables in the statistics, to draw any conclusions concerning the relative therapeutic efficiency of the treatment systems used.

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American Academy of Pediatrics

Proceedings

EIGHTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

HOTEL DEL MONTE, DEL MONTE, CALIF.

JUNE 9, 10, AND 11, 1938

Report of the Executive Board

I wish to submit the following report for the Executive Board of the American Academy of Pediatrics for the year ending May 1, 1938:

The meeting held in Evanston, Dec. 10 and 11, 1937, was the last one with the Executive Board consisting solely of the officers and the regional chairmen. At this meeting associate regional chairmen were appointed, Dr. Stanley Nichols for Region I, Dr. James Bruce for Region II, Dr. Edgar Martmer for Region III, and Dr. Hugh Berkley for Region IV. These associate chairmen in the future will meet with the board. The untimely death of Dr. Louis Schroeder, chairman of Region I, emphasizes the importance of the associate chairmen.

Thirty-three candidates were elected to Fellowship, twenty-four of whom were from Region I. Dr. Alfred J. Scott, Jr., was transferred to Emeritus Fellowship.

The change in the schedule of our annual meetings is significant. Beginning with 1939, the annual meeting will be held in the fall of the year, and the regional meetings in the spring of the year. In 1940 the International Congress of Pediatrics will meet in the United States for the first time. The meeting is to be held in Boston early in September. The close proximity of this meeting and our annual meeting was evident, and possible arrangements were discussed. The question of scheduling the regional meetings just before or after the American Medical Association meeting will have to be decided by the regional membership. Whether this change will increase or decrease the attendance of members of the Academy at the American Medical Association meeting is uncertain, but it is a question which deserves our very definite consideration.

The splendid reception which was accorded the published report of the Committee on Immunization Procedures within the Academy and without indicates the service the Academy can render in this and in similar fields.

The only other matter to which I wish to call attention is the increasing recognition which is being accorded the Academy by all organizations which deal with the child. Evidence of this is brought out by the many requests for cooperation which are received from these organizations.

HENRY F. HELMHOLZ, Vice-President.

Report of the Secretary

There are now 1,229 Fellows in the Academy.

The Secretary is sorry to have to record the death of six of the Academy Fellows during the past year:

Dr. Barnet E. Bonar, Salt Lake City, Utah
Dr. W. O. Colburn, Lincoln, Neb.
Dr. Sylvan D. Lazarus, Brooklyn, N. Y.
Dr. Gustave Lippman, St. Louis, Mo.
Dr. Louis C. Schroeder, New York, N. Y., Emeritus Fellow
Dr. LaFayette B. Mendel, New Haven, Conn.

Special mention should be made of the loss of Dr. Louis C. Schroeder whose devotion to the work of the Academy was in full measure responsible for the success in Region I. Dr. Schroeder was not only loved, but trusted, and his judgment was excellent. The Academy has lost more than it realizes in his death.

Besides the annual meeting, there have been four regional meetings: Region I at Boston, Mass., November 12 and 13; Region II at New Orleans, La., December 1 and 2; Region III at Chicago, Ill., October 14, 15, and 16; Region IV at Los Angeles, November 4, 5, and 6. The Secretary attended all of these meetings and can attest to the excellence of each.

The particular change in the administration of the Academy during the past year has been the elimination of the regional committees and their replacement with associate regional chairmen. This has expedited regional work materially and has also practically doubled the membership of the Executive Board. It is too early yet to say whether this will facilitate action or not, but it will certainly mean a better representation of the membership on that Board.

During the past year two new Committees have been added. The one on Contact Infections whose Chairman is Dr. Fairfax Hall, of New Rochelle, N. Y., has been organized to look into the situation regarding infection through school contacts, and contacts in the school and home especially with regard to teachers and domestics. The second is the Committee on Neonatal Morbidity and Mortality of which Dr. Harold C. Stuart of Boston, Mass., is chairman. This committee was started with Dr. Bonar as chairman, but his untimely death necessitated a revision of the committee which is to cooperate with a like committee from the American Pediatric Society and with the Children's Bureau in Washington.

The other committees have all been quite busy, especially the Committee on School Health and School Health Education, which has put out an excellent questionnaire, and also the Committee on Immunization Procedures, whose booklet you have already received and which has been very popular throughout the country. The Committee on Mental Hygiene has been revised and has decided to take some definite action to proceed with its work.

The Academy has received an offer from Mead Johnson & Company to provide money for a yearly prize. This is being considered by the Executive Board and doubtless will be accepted as soon as a few minor changes have been effected.

At the suggestion of the members of Region II, concurred in by the members of Region III, the Executive Board has recommended that hereafter the annual meeting be held in the fall and the regional meetings in the spring.

There is an ever increasing interest among the various state groups in the work that is being carried on in the states. This does not appear officially but is nevertheless a very important part of the work the Academy is doing and should be supported in every way by the members. It is surprising how much there is to do if we look for it. Oftentimes the states that have the smallest membership are the most active in getting things done. In many of the larger eastern states there has been a complacency which is certainly not justified.

In a recent letter, the American Medical Association offered to send typewritten lists of physicians who limit their practice, or give special attention to certain specialties. It is interesting that of the single groups, the first group is surgery with 13,696; the second group, internal medicine, 4,797; and the third group, pediatrics

with 4,086. It is true that the group of specialists practicing both obstetrics and gynecology numbers 6,886; ophthalmology, otology, laryngology, and rhinology a total of 8,451. However, for the definite groups pediatrics ranks third and is just behind internal medicine.

Respectfully submitted,

CLIFFORD G. GRULEE, Secretary-Treasurer.

Report of Region I

In Memoriam

It is with sorrow and regret that Region I must report to the Academy the loss of its regional chairman, Dr. Louis C. Schroeder, of New York City, who had been chairman of Region I since the beginning of the Academy.

Dr. Schroeder gave a lifetime of devotion to the cause of child health in many fields. As chairman of Region I he was an inspirational leader and a friendly companion to every state officer and Fellow of the Academy.

It was characteristic of Dr. Schroeder that, when ordered by his physician, because of heart trouble, to give up all his general activities, he was quoted as saying to his secretary, "Send in my resignations to all of my other positions, but maybe I can find a little time for the Academy work, as it means so much to me."

Such a spirit cannot help but inspire all of the officers and Fellows of Region I to better service to the cause of child health. As a memorial to his untiring efforts and kindly leadership we will build a better structure because of the splendid foundation he has laid for us through the years.

Before presenting a bird's-eye view of the progress which has been made during the past year in each of the states and provinces of Region I, we would like to make a few observations as to the general pediatric situation in the region.

In all of our states and provinces there has been a steady growth of the influence of the Academy Fellowship in stimulating improvement in all forms of Child Health Service and bettering the medical status and pediatric knowledge of both the pediatrist and the general medical profession.

Section I of Article III of the Constitution of the American Academy of Pediatrics reads thus:

> "The object of the Academy shall be to foster and *stimulate interest* in *pediatrics* and *correlate* all aspects of the work for the welfare of children which properly come within the scope of pediatrics."

In other words, that the Academy shall—

(a) *stimulate* scientific pediatric knowledge

(b) *co-ordinate* Child Health Services in each state and province of the Academy.

We have listed below fifteen possible state academy activities, and we note by the reports of our state chairmen that in every state and province there has been, during the past year, a great deal of expansion in many of these fields. A much larger number of the Fellows of the Academy in each state are actively participating in the promotion of scientific pediatric knowledge and stimulating the various forms of better child health service. This is most encouraging evidence of sound growth and proves beyond doubt the continuing need of the leadership and guiding hand of the American Academy of Pediatrics in all of the facets of that evergrowing structure called "child health service."

Some of our states with larger membership have been able to develop most of these fifteen fields listed, while some states with fewer members have selected those activities which seemed to be most needed in their own districts. All have been active and are to be commended for their work and devotion to the general objectives of the Academy.

While it is not possible for a tail to wag a dog, it is perfectly possible and feasible for the American Academy of Pediatrics to be the "Thinking and Planning Child Health Lobe" of the brain and the "All-Seeing Child Health Eye" of the medical profession and governmental and welfare departments, as well as functioning similarly for nonofficial agencies dealing with some phases of child health.

Our national and state organizations of the American Academy of Pediatrics have proved their great value by providing leadership and active expert assistance in the coordination of the various child health services rendered by these several groups, and are the one medical body capable of doing this most important of all child health jobs.

How extensively this is being done in the various states and provinces in Region I, will be shown by the highlights of our state chairmen's reports covering the following list of Academy activities in some of our states.

It is clear that all of our state groups have realized the importance of *coordinating* and *stimulating* the *existing* official and nonofficial agencies dealing with Child Health and the *promotion* of pediatric knowledge among pediatrists, general practitioners and the public groups.

The most important single activity of any state Academy Fellowship is to act as the stimulating, coordinating keystone of child health development for both the state medical society and the state department of health. This is fully realized by our state chairmen. Most of the other important activities of the Academy can be built on this three-organization child health arch, when so erected.

With this clear understanding of our state chairmen of the objectives of the Academy and promotion of its ideals, Region I is looking forward to a year of increased usefulness to child health, by both improving the position of the pediatrist and rendering better child health service to the public.

State Activities

Outline of Academy Activities in Some of Our States and Provinces

A. Improving Pediatric Knowledge—
   1. Helping our Fellows solve scientific pediatric problems
   2. Helping our Fellows solve pediatric practice problems
   3. Postgraduate education of
      a. Pediatricians
      b. General practitioners

B. Child Health Activities: Promotion and coordination of better child health service
   4. Child Health activities in connection with state medical societies
      a. Maternal welfare section—
         Prenatal care
         Good obstetrics
         Maternal nursing
      b. Pediatric section—
         Care of the newborn infant
         Preschool age child
         School age child
         Adolescent

5. Child health activities in connection with state departments of health.
   a. Bureau of Child Hygiene and Maternal Health
6. Child health activities in connection with state welfare departments.
   a. Health of dependent, handicapped and neglected children, etc.
7. Child health activities in connection with state departments of education
   a. Health of school age child
   b. Mental hygiene
   c. Adolescent problems
8. Child health activities in connection with other state official and nonofficial groups dealing with some phases of child health work.
9. Contagious disease facilities in hospitals and pediatric facilities in hospitals.
10. Control of communicable diseases.
11. Promoting routine child health supervision by

    a. Pediatricians
    b. Family physicians

    } during { infancy / preschool age / school age / adolescence

12. Mental hygiene and adolescent problems.
13. Tuberculosis control in childhood.
14. Safety of children during childhood.
    a. Auto and home accidents, burns, poisons, etc.
15. Health of children in summer camps.

Report of Region II

A survey of the activities of Region II for 1937 and 1938 reveals that it has made some progress. Although the region reported only three applications for membership, it must be remembered that the number of those who are qualified is limited. At the present time we have 243 members, with the prospect of a few more; only 15 remain who have an American Board of Pediatrics certificate. The states of Arkansas, Alabama, Louisiana, Mississippi, Oklahoma, and Virginia will have no more prospects until some of the younger men are able to fulfill the requirements of the American Board of Pediatrics.

Every state chairman has been working with the established agencies throughout the states, the plan being to coordinate the various pediatric activities, to eliminate the weak ones, to assist the strong ones, and to attempt to interest those concerned with child health problems in certain definite projects, so that the work will not overlap. Each state in the South has a pediatric society, which is working in conjunction with the state medical society.

Refresher courses are being given in the majority of the southern states. Florida, Georgia, Kentucky, Mississippi, North Carolina, Oklahoma, South Carolina, Texas, Virginia, and West Virginia have well-established programs, either under control of the state medical society or the state health department.

As a complete résumé of the activities of this region is presented in THE JOURNAL OF PEDIATRICS, April, 1938, a more detailed description is unnecessary.

This region voted unanimously that the national meeting of the Academy be held at a separate place and at a separate time from that of the American Medical Association, also, that the regional meeting be held separately from that of the Southern Medical Association. It was the consensus that both the Academy and the respective sections would be benefited by this change. The members of the Academy of this region who were present pledged their allegiance to the pediatric sections of the American Medical Association and the Southern Medical Association; all felt that the Academy members should be the leaders in these sections. It was

also the general opinion that the programs in these sections should be practical, arranged primarily for the general practitioner and others interested in pediatrics, rather than for the specialist in this field. Further, it was agreed that all those interested in pediatrics be invited to the meeting of Region II and that this program consist of clinics as well as round table and panel discussions.

During his six years in office the regional chairman has visited most of the states in the region. There seems to be harmony and a good spirit among the Academy members, although there is still a feeling that the "rank and file" do not have a sufficient part in Academy policies. Many of the members appear willing to allow a few to do all the work. This materially limits the possibilities of the group.

The chairman would recommend that there be a meeting of all the members of the Academy at least once each year in each state; that there be no program, but rather, a full, free discussion of all the pediatric problems in that state; that committees be appointed by the state chairman to see that every Academy member in that state has some active part in its work. When this is accomplished, there will be no difficulty in securing the fifteen eligibles in this region who are still not members of the Academy. Solicitation of members is believed to be a bad policy; the Academy should demonstrate by its accomplishments that it is of more value to any man than that man is to the Academy.

It is also recommended that the state chairmen request every man in the state to pass either favorably or unfavorably upon every applicant from that state. If this were done in writing, there could be no later criticism, as has occurred in many instances.

I believe the change from the regional board to an associate chairman was a happy solution of some of our difficulties. I am especially pleased with the selection of Dr. James Bruce, of Louisville, as associate chairman of this region. We have discussed in detail the policies of the region, and I feel that his counsel will be of great assistance to me as its chairman.

In closing, I believe it is being demonstrated throughout the entire United States that the Academy was organized for a good purpose. The principles of the organization are sound, and its possibilities will be unlimited when all members become actively interested.

I wish to thank the state chairmen for their cooperation during the past year.

Respectfully submitted,

E. C. MITCHELL,

Regional Chairman.

Report of Region III

On Oct. 14, 1937, a meeting of the state chairmen of Region III was held at the Lake Shore Athletic Club, Chicago. Dr. A. Graeme Mitchell, Regional Chairman, presided. There were present the following: Dr. Franklin P. Gengenbach, Colorado; Dr. Maurice L. Blatt, Illinois; Dr. E. G. Padfield, Kansas; Dr. Edgar E. Martmer, Michigan; Dr. E. J. Huenekens, Minnesota; Dr. Park J. White, co-chairman from Missouri; Dr. Ralph E. Pray, North Dakota; Dr. Sterling H. Ashmun, Ohio; Dr. Goldie E. Zimmerman, South Dakota; and Dr. Abraham B. Schwartz, Wisconsin.

Dr. E. W. Hancock represented Dr. Clyde Moore, Nebraska, who was unable to attend. Dr. Frederick B. Miner, Flint, Mich., was present by invitation.

Several state chairmen presented reports of the activities in their states.

The following applicants were recommended by the regional committee to the Executive Board for election to membership:

Dr. James J. Donahue, E. St. Louis, Ill.
Dr. Clair L. Douglas, Detroit, Mich.
Dr. Ernest Ekermeyer, Xenia, Ohio
Dr. Faith F. Hardy, Grand Rapids, Mich.
Dr. Harold O. Lund, Middletown, Ohio
Dr. John W. Maroney, Detroit, Mich.
Dr. Mark F. Osterlin, Traverse City, Mich.
Dr. Thomas P. Saltiel, Chicago, Ill.
Dr. Clara D. Tigay, Chicago, Ill.
Dr. Dwight A. Weir, Mansfield, Ohio

There was discussion of the matter of applicants who did not confine their practice to pediatrics. It was moved by Dr. Martmer and seconded by Dr. Pray that it be recognized as a plan of Region III that no applicants should be recommended to the Executive Board who did not limit their practice to pediatrics unless such applicants were engaged in a type of work which, because of specific circumstances, demonstrated a direct contribution to pediatrics.

On motion by Dr. Martmer it was recommended that there be a suggestion from Region III to the Executive Board that the Academy of Pediatrics make some study, perhaps by the appointment of a committee, in regard to the thymus gland. It was suggested that this might take the form of a round table discussion or a panel discussion at one of the Academy meetings. It was felt that, if it were possible for some definite statement to be made, even if negative in nature, regarding symptoms produced by the thymus gland, it would be helpful.

Dr. Martmer invited Region III to Detroit in 1938 for the next annual meeting. This invitation was immediately accepted and it was decided that the time of the meeting would be settled by the Michigan group.

There was discussion of recommendations for associate regional chairman. The regional chairman stated that he would get the opinion of each state chairman by letter, and it was moved that he then take these recommendations into consideration and recommend directly to the Executive Board the names of two candidates, one of whom would then be chosen by the Executive Board as an associate regional chairman.

Dr. Krafft, of Chicago, was allowed the floor. He wished to call the attention of the regional committee and of the Academy of Pediatrics to the underprivileged (precriminal) child. He thought that contacts should be made with educational organizations and with lay societies and organizations; that the physicians as well as the laity should be educated in the problems involved; that all children should be examined annually; that efforts should be made to secure legislation concerning these subnormal persons. It was the opinion of those at the meeting that many of these contacts were already being made in different states and that no particular recommendation need be made by the regional committee to the Executive Board.

The regional chairman, after communication with the various state chairmen and upon the basis of this, recommended to the Executive Board the names of two candidates, one of whom was to be chosen by the Executive Board for associate regional chairman. Of these two candidates, the Executive Board chose Dr. Edgar E. Martmer for associate regional chairman.

Region III of the Academy will hold its regular meeting in Detroit on October 27, 28, and 29. The arrangements for this meeting are under the charge of Dr. Edgar E. Martmer of Detroit.

A. GRAEME MITCHELL
Regional Chairman

EDGAR E. MARTMER
Associate Regional Chairman.

Report of Region IV

The membership of Region IV has reached a fair degree of saturation. There are now 120 members including a very high proportion of those doing exclusively pediatrics.

This membership is well represented in all that is being done in pediatrics in the West, including the administration of child welfare activities supported by federal social security funds. In several of the states the directors of child and maternal welfare are members of the Academy.

The tragic and untimely death of Barnet Bonar is sincerely mourned by the entire Region. He brought great ability and kindly personality to the practice of pediatrics. His loss will be a great one to pediatrics of the West.

The annual regional meeting was held last fall in Los Angeles. About two-thirds of the regional membership was in attendance, a most interesting and well-arranged scientific program was presented and arrangements for the comfort and entertainment of visitors left nothing to be desired.

This year, in order to concentrate interest in the Del Monte meeting, there will be no additional meeting of Region IV. It is our sincere wish that the first western meeting of the Academy shall be so pleasantly remembered as to be soon repeated.

EDWARD B. SHAW,
Regional Chairman.

SPECIAL COMMITTEE REPORTS

Report of the Committee Appointed to Study the Age Limits of Pediatric Practice

The Committee Appointed to Study the Age Limits of Pediatric Practice submits the following report for the consideration of the Executive Board and membership of the American Academy of Pediatrics.

It is the consensus of your committee that it is impractical to establish a definite age limit for pediatric practice. The practice of pediatrics begins at birth and should extend through the adolescent period. In most instances, the termination of pediatric practice would be between the sixteenth and eighteenth years of life.

Respectfully submitted,

EDGAR E. MARTMER, Chairman
STERLING H. ASHMUN
PHILIP M. STIMSON
HAROLD C. STUART
MELDRUM K. WYLDER

Report of the American Board of Pediatrics

The members of the American Board of Pediatrics appointed by the American Academy of Pediatrics submit the following report of the work of the board for the year 1937-1938.

Five examinations have been held; at Atlantic City (June), Chicago (October), Los Angeles (November), Boston (November) and New Orleans (December). In all, 182 candidates were examined, of whom 69.34 per cent passed and have been certified; 21.87 per cent failed, and 8.79 per cent were conditioned. To date, May 1, 1938, 1,226 certificates have been issued by this board.

In addition to the six announced in last year's report, Dr. Hugh Berkley and Dr. Victor Stork, of Los Angeles, have been appointed official examiners for the board.

At the meeting of the Advisory Board for Medical Specialties held in Atlantic City in June, 1937, it was decided to obtain funds to make a general survey of

graduate medical education in the United States. A foundation grant of $75,000 has been obtained, and the survey is under way. Dr. Blackfan is the pediatrician appointed to the committee in charge of the survey.

Boards have been organized and are at work in all the twelve special fields recognized in the agreement between the advisory board and the Council on Medical Education of the American Medical Association.

A proposed biographical directory of the licentiates of all twelve boards has been postponed, awaiting the completion of the on record certification of the Boards of Medicine and Surgery.

The American Board of Pediatrics is compiling an address booklet of their licentiates.

No changes have been made in the membership of the board.

Respectfully submitted,

HAROLD C. STUART
BORDEN S. VEEDER
ALFRED A. WALKER

Report of the Committee on Child Health Relations

During the past year the Committee on Child Health Relations of the American Academy of Pediatrics has pursued its policy of stimulating a close cooperation between members of the Academy in each state and those agencies administering the three phases of the Social Security Act with which we are chiefly concerned; namely, maternal and child health, child welfare, and the crippled children's program.

Representatives of this committee have been appointed in forty-five states. Your committee has requested the Children's Bureau to forward to each of its representatives pertinent data pertaining to activities of the social security program, and any other material concerned with maternal and child health which it seemed would be of interest and aid to members of the Academy in their work in these fields. From the expressions of appreciation coming from the various states, the committee feels that this has been a very definite service and wishes to express the thanks of the Academy to the Children's Bureau.

A résumé of the activities of the members of the Academy in matters of maternal and child health, particularly as related to the program made possible through the Social Security Act, is included in this report. So many requests have been received, asking about programs in other states, it was thought advisable to give these in some detail.

The reports, as a whole, indicate that the Academy is very definitely interested in the program and ready to cooperate in any way possible. In many instances, however, members have not taken the initiative but have waited until their services have been requested by the various state agencies. One gains the impression in reading these reports that in many states there seems little desire on the part of these agencies to enlist the aid and advice of the Academy. Your committee feels that the Academy should initiate a more active program in its efforts to guide the various federal and state agencies working in the maternal and child health fields.

There is practically no evidence of Academy activity in the child welfare and crippled children's programs.

The committee feels that there is great need for integration of the maternal and child health activities carried on by the various lay and professional organizations in the states. When such coordination has been attempted, very definite benefits have

accrued. This is particularly true in the rural sections. The Academy might well be the motivating force in initiating such a program.

Respectfully submitted,

M. HINES ROBERTS, Chairman
PHILIP F. BARBOUR GEORGE M. LYON
W. L. CRAWFORD STANLEY H. NICHOLS
MARTHA M. ELIOT OSCAR REISS

Resumé of Activities

California.—Three physicians are members of the professional advisory committee on maternal and child health. Three meetings during the year were held.

May, 1937: General outline of activities, forms and literature of the Bureau of Child Hygiene. Revision of a first-aid kit for rural schools. Possibility of professional education discussed.

November, 1937: Progress and activities of staff in the field during past six months.

January, 1938: Discussion of May Day Child Health Day. Lay advisory committee convened in joint session to work out relationship between professional and lay groups in rural areas and to promote organization of county committees. Dr. Shaw, Dr. Sweet, and Dr. Reiss participated in perigrinating orthopedic clinics. Dr. Sweet will hold clinics in Idaho, April 27 to May 3. Dr. Shaw expresses need for medical agency to coordinate child health activities, lay and professional.

Colorado.—Dr. Friedman reports that he has not been called upon to render medical service by any of the state agencies.

Iowa.—Two members act as consultants to the department of health in planning and administering funds in rural areas. Three members serve on Committee on Maternal and Child Health of the Iowa State Medical Society. A plan of considerable interest is the establishment of stations for the care of premature infants at strategic centers. Advice in preparation of programs of lay organizations. Pediatric clinics for general practitioners.

Certain members are opposed to any attempt to bring all lay and professional groups together in an integrated state and county program.

Louisiana.—Refresher courses in pediatrics in Mississippi, Louisiana, and Florida.

Maine.—Dr. Foster is chairman of the Advisory Committee on Maternal and Child Health, serving with three other members of the Academy. Refresher courses in pediatrics, obstetrics, and orthopedics. Physicians apathetic to program.

Georgia.—Two physicians are on Advisory Committee on Maternal and Child Health. Activities in the main are directed toward stimulating action in child health and welfare councils through the state. These councils are composed of lay and professional groups concerned with maternal and child health. Dr. M. Hines Roberts is a member of Advisory Committee of Child Welfare program. One meeting was held. Dr. Roberts was recently appointed by president of the Medical Association of Georgia to serve as a member of the Technical Advisory Committee of the Crippled Children's Service. No meeting as yet.

Maryland.—Dr. Knox states that he has received assistance from members of the Academy from time to time in promoting maternal and child hygiene.

Michigan.—The Academy is represented on preventive and maternal health committee of the state medical society. Prepared standard immunization schedule for state use.

Postgraduate program in conjunction with Michigan State Medical Society, University of Michigan, and Wayne University. Refresher courses under sponsorship of state director. Radio programs.

Minnesota.—Refresher courses for physicians and public health nurses. Cooperation with the state department of health in coordinating maternal and child welfare projects motivated by various professional and lay groups.

Missouri.—Dr. Dwyer is on Advisory Committee of Child Health division of state department of health. His services have never been requested. The Academy has no representation on state medical association's committee on maternal and child health. No pediatrician on this committee. Cooperation with P.T.A. campaign for examination of every school child before admission to school. Every child examined by own physician for $2. Trying to dissociate medicine and schools. Avoid introducing persons to well-baby stations and dispensaries.

Montana.—Conference with state department of health on maternal and child health. Examination of all preschool and government nursery school children for past two years with cooperation of state department of maternal and child health. Considerable opposition within state medical society to program.

Nevada.—Advisory to maternal and child health program under state department of health.

North Carolina.—Dr. Root serves on Advisory Committee on Maternal and Child Health of state board of health. This committee meets quarterly. Certain representatives feel need for integration of maternal and child health activities of various professional and lay groups in the state and county.

New Hampshire.—Cooperation with lay groups in their programs. No official status of Academy members in the social security program is reported.

New Jersey.—Representation on public health committee and Advisory Committee on Child Health and Maternal Health of the medical society of New Jersey. Lectures on preschool age group arranged by members of Academy, financed by social security funds.

North Dakota.—Academy members on Committee on Maternal and Child Welfare of North Dakota State Medical Society. No close cooperation between this group and the state department of health.

Feel that an effort to coordinate program of various professional and lay organizations on maternal and child health is definitely needed.

Oregon.—Dr. Henricke is chairman of the Committee on Clinic and Institutional Medical Care of the state medical society; he works in close cooperation with Division of Maternal and Child Hygiene of the state department of health. Strongly favors closer coordination of child health and welfare activities of lay and professional groups. The apathy or opposition of the general practitioner makes the program difficult.

Pennsylvania.—Academy members in cooperation with the Pennsylvania Medical Society have initiated an extensive maternal and child health program. Under the auspices of the county medical societies 59 counties have organized child health work. All agencies concerned with child health in the county have been drawn into the program. The Academy group has attempted to cooperate with the department of health and the maternal and child health program of the Children's Bureau. It feels, however, that a simpler medium and program than that of the maternal and child health service of the Children's Bureau is needed.

South Dakota.—Academy members are not active in support of agencies administering the Social Security Act.

Tennessee.—No report received of official activities of Academy members in the social security program.

Texas.—Academy members cooperate in child health lectures.

Vermont.—Cooperation with state department. Lectures before county medical societies.

Virginia.—In cooperation with state medical society and pediatric society recommend legislation for adequate care of tuberculous children, better teaching facilities for the mentally subnormal, and more widespread immunization of the indigent. Offered services to state agencies, but they have not accepted such service.

Washington.—Members of Academy cooperate with Committee on Maternal and Child Health of the state medical association in conducting programs in various county medical societies. Two members of Academy made nutritional survey, receiving help from "Aid to Dependent Children." State chairman of Academy is relieving physicians in charge of maternal and child health program of the state health department and organizing group to coordinate activities of various lay and professional organizations in matters of maternal and child health. Academy members assist in postgraduate lecture program.

West Virginia.—Four members of Academy serve on Committee on Child Health of the state medical association. This committee in close cooperation with state in developing refresher courses, preschool conferences and an educational program including posters, radio, etc. Approves effort to integrate activities of various lay and professional groups concerned with maternal and child health.

Wisconsin.—Dr. Peterman giving refresher courses in Montana.

Report of the Committee on Clinical Investigation and Scientific Research

The Committee on Clinical Investigation and Scientific Research has considered the generous offer of Mead Johnson & Company to donate funds yearly for prizes to be awarded to young research workers. Your committee concludes that the administration of this work is not one of its functions and believes that a special committee should be appointed by the Academy to perform these duties. The committee would like to draw the attention of the Academy to the fact that it would be to the advantage of the Council for Pediatric Research if the money thus donated passed through the hands of the council.

The committee further recommends that the proposed investigation as to the cause of rickets, etc., be turned over to the Council for Pediatric Research for administration of funds and direction of the research.

Respectfully submitted,

FRITZ B. TALBOT, Chairman
WILBURT C. DAVISON OSCAR SCHLOSS
HENRY F. HELMHOLZ FRANCES SCOTT SMYTH

Report of the Committee on Contact Infections

Pediatricians have always shown themselves willing and anxious to take an active part in a program designed to benefit the health of the community and that of their patients. Close association of a child with a person having an unrecognized communicable disease is a potential source of infection for that child. The adults with whom children are most constantly in contact are parents, other members of the family, school teachers, and domestic employees. Although parents are the most intimate associates of children, the employees in a home are the persons about whom the least is known from a health standpoint. When nursemaids and houseworkers are engaged to help with the care of children, it should be known, that they are free from transmissible infections.

The diseases not infrequently transmitted by adults to children in their environment are tuberculosis, syphilis, gonorrhea, typhoid by carriers, and respiratory and skin diseases. The most important and the most dangerous for children is tuberculosis. It is well known that a case of open pulmonary tuberculosis without proper control in a home will infect every child there. It is against this disease

that the greatest amount of protection for children may be expected by a proper physical examination of the adults to whom they are exposed. Since a roentgenogram of the lungs will detect the presence of any existing pulmonary tuberculosis, even in an uninfectious stage, it is essential that this be a routine procedure in examining adults for the protection of children.

It is extremely important that parents have no infectious diseases, not only for their own sakes but for their children's. Moreover, in order to obtain the cooperation of a domestic worker in having a medical examination, it is always desirable that the employers should have had a similar examination themselves and hold a certificate from the family physician, so stating. It is often necessary to set this example and use it as an argument in order to persuade some domestics to be examined.

If any great number of adults are to provide themselves with periodic health examinations, or if servants are to be willing to do so at the request of their employers, a great deal of effort must be put forth. An intensive campaign of education is necessary. The employers of domestic workers must learn to be discriminating in regard to the health of servants they engage to assist in the care of their children. Publicity must be sufficient to reach the domestic class in order to overcome prejudice against being examined and obtaining health cards. It must be pointed out to workers that the advantages gained by periodic examinations are not of health value alone but economic as well. Public opinion must be created to make health references as commonly asked for, and furnished, as character references. Pediatricians know the need for this and are in a position to be the greatest influence towards its accomplishment.

Experience in Westchester County, N. Y., with a plan to make this possible has been very encouraging. It has been received favorably both by doctors and by parents who employ household help. Many of the more influential women's organizations, public health societies, Parent-Teachers' Associations, and men's service clubs have been active with the publicity and education campaign. The Metropolitan Life Insurance Company has offered to aid the campaign among its policy holders in Westchester County.

The principle of periodic health examination was acceptable to the Medical Society of the County of Westchester. The medical aspect of the program has been sponsored by the society and its public health committee has arranged a standardized examination form for domestics. The members of the society have been requested to make this examination at a low fee. Roentgenologists have agreed to take a single film exposure of the chest for $3, and the blood Wassermanns are done by the state laboratory free of charge.

Even in this locality there remains much to be done. The public should be made more fully aware of the advisability of periodic health examinations. There still is opposition toward the idea on the part of some servants, and more effort is needed to secure the cooperation of employment agencies. The pediatrists should be encouraged to continue this effort they have begun to safeguard their patients.

Much headway has been made with this campaign in Knoxville, Tennessee. In that city 12 cases of active tuberculosis and many syphilis and 5 typhoid carriers were found in routine examination of domestics in the past year, In Newark, N. J., health cards have been required for several years. In North Carolina and other parts of the south, this matter has been given serious attention.

The Committee makes the following recommendations to the American Academy of Pediatrics:

1. Acquaint the members of the Academy with the advisability of recommending a thorough periodic physical examination to all adults in close contact with children.

2. Attempt to influence parents to have periodic examinations themselves for the protection of their children and as an example to their employees.

3. Ask pediatricians also, to have physical examinations in order to set a proper example and to create the impression that they believe in what they advise.

4. Encourage the x-ray examination of the lungs of teachers and other school employees.

5. Take steps to initiate a campaign for the education of the public regarding the need for, and value of, such examinations. Develop public opinion to the point where it becomes customary for domestic workers to hold medical cards as a "health reference" as the result of having undergone the necessary physical examination.

6. Get the cooperation of employment agencies to encourage domestics, who work in families with children, to obtain "health cards."

7. Enlist the assistance of child health-minded organizations, in as many communities as possible throughout the country, to carry out this campaign.

8. Secure the cooperation of local and county medical societies throughout the country to adopt a standardized examination which will detect evidence of communicable disease. (An x-ray of the lungs is requisite.) The charge for these examinations must be sufficiently low as to be within the ability to pay, of all who need them.

9. It is further recommended that subcommittees be appointed in each regional district to carry on this work in their localities.

Respectfully submitted,

FAIRFAX HALL, Chairman
GAYLORD W. GRAVES
REGINALD A. HIGGONS
OLIVER W. HILL

Report of the Committee on Cooperation with Nonmedical Groups and Societies

At the beginning of the year 1938, Dr. Henry F. Helmholz found it necessary to relinquish the chairmanship of this committee owing to the pressure of other duties. The present chairman was named by the president, Dr. Philip Van Ingen, to fill Dr. Helmholz' unexpired term. It is regrettable that the original chairman found it impossible to continue in charge of the committee which was created at his suggestion and for which he envisoned an increasingly important role in the affairs of the Academy. It is the hope of the remaining members of the committee that they may, in some measure at least, be able to bring their activities to the plane of usefulness Dr. Helmholz had in mind.

During the year the Committee has continued its cooperative efforts with the American Camping Association. On December 11, Dr. Henry E. Utter attended a meeting of the New England Camp Directors' Association at Boston, and on December 18, the Conference of Consultants of the American Camping Association Research Committee at New York. Dr. George F. Munns attended a conference of the latter group at Ann Arbor in November in place of Dr. Albert D. Kaiser who was ill at the time. A third meeting which was scheduled to be held in Chicago in February was postponed to some future date. The purpose of the conferences was to develop a research program for the study of camp practices leading to the establishment of certain standards and codes. It was suggested that the Academy might be in a position to influence the diversion of some of the funds granted to states under Title V of the Social Security Act to assist in carrying out the study. However, since the postponed conference has not as yet been held, the committee has no conclusions or recommendations to offer at present.

Recently contact has been made with Dr. Lillian Smith, National Chairman of the Summer Round-Up of the National Congress of Parents and Teachers. The movement sponsored by this organization is of interest to all members of the Academy. As yet, the committee has no formal cooperative program to recommend, but a suggestion, which Dr. Smith felt would be of considerable value, might be made that each state chairman appoint a committee of Academy members to confer with state and local summer round-up officials. One of the urgent needs of this lay group is an effective means of interpreting its program to the medical organization. In the capacity of a go-between, with the lay officials on the one hand and the medical profession on the other, such a committee should be able greatly to facilitate and enhance the program of this important national organization. The committee would make the further suggestion that state chairmen who think the plan feasible for their states, notify the chairman of this committee in order that he may forward the names of the Academy members selected to Dr. Smith. She in turn will advise the state summer round-up officials of the personnel of the committee available for cooperation.

The only other activity undertaken by the Committee in the past year was the reviewing and submitting of criticism of a brochure entitled "A Health Program for Children in Foster Care," prepared by Dr. Florence A. Browne, pediatrician for the Child Welfare League of America. The brochure is a brief outline of the various parts which together make up a complete health program. It is intended as a guide to agencies harboring foster children in determining the adequacy or inadequacy of the health services available for their charges.

Respectfully submitted,

LEE FORREST HILL, Chairman
DENNIS H. KELLY, Secretary
C. A. ALDRICH — ALBERT D. KAISER
JAMES W. BRUCE — HENRY E. UTTER
MARGARET I. HANDY — NORMAN C. WETZEL

Report of the Committee on Hospitals and Dispensaries

The Committee on Hospitals and Dispensaries has recently finished a report concerning the question of age limits in pediatric hospitals and in pediatric divisions of general hospitals.

This report represents a consensus of opinion with respect to this and related questions among twenty-eight men who head children's hospitals in this country and Canada. Data were received by the questionnaire method and the report will be published in detail later.

Respectfully submitted,

GEORGE F. MUNNS, Secretary
CLIFFORD G. GRULEE, Chairman
MURRAY H. BASS — HENRY DIETRICH
LAURENCE R. DEBUYS — LEWIS WEBB HILL

Report of the Committee on Immunization Procedures

The secretary of the Academy has submitted a copy of the report of the Committee on Immunization Procedures to each member of the Academy. No member of this Committee feels that this report was perfect or that it represented the last word on the subject. Additions, corrections, modifications, and improvements will be necessary.

In this report, the last sentence under "Rabies" should be deleted and the following sentence substituted: "This, however, is not so important as the fact that recovery from this disease is rare."

The members of the Academy are requested to aid us and send any suggestions or criticisms they may have to any member of the Committee. Such data will be analyzed and evaluated in the light of available controlled evidence. If the data is voluminous, another preliminary report would be forthcoming either at the semi-annual meeting of the Executive Board in December or at the annual meeting in 1939.

Respectfully submitted,

JOHN A. TOOMEY, Chairman
HORTON CASPARIS — BÉLA SCHICK
E. J. HUENEKENS — EDWARD B. SHAW
CHARLES MCKHANN

Report of the Committee on Infantile Paralysis

The Committee on Infantile Paralysis has not held a meeting since its last report, since there seemed to be no particularly good reason for it. The chairman of the committee, however has been in contact with Mr. Basil O'Connor, the president of the new National Foundation for Infantile Paralysis. Certain advice was given which at this stage related only to the fact that this new committee should have an advisory medical council. The recommendations or, rather, suggestions, were made concerning the personnel of this advisory committee.

Last year it was suggested that this Committee on Infantile Paralysis of the Academy cease to function. At the present moment it is suggested that it might be well to continue this committee since possibly it may have some function in the next year or two.

Signed,

A. GRAEME MITCHELL, Chairman

Report of the Committee on Medical Education

Postgraduate Education.—Reports were received from all but three of the states in regard to extramural postgraduate courses in pediatrics. Questionnaires were sent to all state chairmen and to all directors of maternal and child health.

An outstanding feature was that during 1937 there was a marked increase in the active interest of state chairmen and of individual Academy members in this activity. Discussions accompanying the returned questionnaires evidence a greater understanding on the part of state chairmen not only of the objectives of such programs, but also of the difficulties encountered in the mechanics of organization of such courses and their bearing on the degree of success subsequently achieved.

Programs of outstanding accomplishment during the year were conducted in Iowa, Minnesota, Michigan, Wisconsin, Mississippi, Virginia, Massachusetts, and Texas. Many other states initiated programs during the year, and still others, recognizing the weaknesses in their technic of organization, are now making improved plans directed toward a more effective interest and attendance in the programs to be attempted in the future.

It is apparent from the brief experience at hand that no one type of plan will be universally successful. It is equally apparent that no matter how good the instructor, the course cannot succeed as well as it should unless there is the proper organization preceding it. At the moment the chief problems confronting those attempting to develop such extramural postgraduate courses lie not in the selection of proper instructors, or in the content of material given, but in the selection of the proper type of course for the locality to be served, satisfying therein as well as possible those variables which may work for or against the success of the course and which are of almost equal importance in the matter of the development of an in-

creasingly more effective organization and build-up. The most common adverse comments encountered in the replies received would seem to be fairly well covered by the implications embodied in the suggested outline for organization, which was prepared and submitted to all directors of maternal and child health and to all state chairmen of the Academy. Much is yet to be learned, however, in regard to methods of organization.

During the year there was increasingly more utilization of such interest-increasing techniques as (1) personal consultations, (2) check lists for demonstrations of clinical and therapeutic procedures, (3) informal out of hour discussion, (4) talks to lay groups in attempts to advance the understanding of child health protection locally, and (5) better preliminary organization and build-up with proper regard to specific local characteristics, such as number of physicians in district served, season of year, geographic and economic characteristics of the community, etc.

There seems to be an increased tendency at least in some states to integrate the program with that of the extension department of a medical school or of a state university. This is probably a logical and constructive procedure. It is certainly true that many state medical society committees on postgraduate education are not active enough to put over properly the organization and preliminary build-up generally so essential to a proper development of such courses. Some committees have not sensed the specific needs for, and objectives of, these courses, while others because they are of necessity only volunteer part-time workers, cannot devote to the program and its development the time and effort so necessary to make it successful. There is a logical reason why such state or regional committees can be expected to serve effectively in an advisory capacity, but it is not so logical to expect them to provide the personnel so essential for visiting local physicians, explaining to them the objectives and nature of the course, obtaining enrollment in course, etc. These essential details of the executive administration must have proper treatment. It has been repeatedly observed that it takes more than personal letters from the president of the state society, the president of the local county society and the chairman of the local committee to provide a preliminary build-up. Programs that depend primarily upon such a foundation for their build-up will generally not be very successful. There is real need for a definite executive agency being integrated with the program. The state health department does not seem to be the agency most ideally suited to the best execution of this part of the program.

Throughout the questionnaires a significant statement appears with amazing regularity. It is to the effect that the local chairman is the keyman in the success of such a program. It is intimated repeatedly that rarely can a course have a successful attendance unless the local keyman does provide the proper build-up preceding the course and provide proper assistance throughout the conduct of the course. He is the one who has had to be responsible for getting the attendance and he is the one to bring the instructor and physicians attending the course ever more intimately together. Unfortunately it is not always possible to have good keymen. It is therefore desirable to work out a procedure that is not dependent upon a local leader to put it across successfully, at least the local man must not have to do it all.

For those interested in developing such courses or for those acting as instructors, the committee has on file an interesting collection of letters, outlines, and brochures. From this data at all times the chairman will be glad to supply, on request, such aid as Academy members may desire.

Respectfully submitted,

George M. Lyon, Chairman
Horton Casparis
Hugh L. Dwyer

Report of the Committee on Mental Hygiene

The Committee on Mental Hygiene feels that the mental growth and development of the child and all of the factors which influence it favorably or unfavorably are as much the responsibility of the pediatrician as is the physical growth and development and all the factors which influence it favorably or unfavorably. The pediatrician is the sole consultant of parents concerning physical and mental health problems during the preschool period and should continue as the chief consultant during the remainder of childhood and adolescence.

Medical schools and training centers have, in general, failed to provide adequate training in mental growth and development and mental hygiene problems of children for medical students or pediatric interns and residents. Less than 50 per cent of the medical schools give any instruction in pediatric psychiatry. Very few hospitals give the pediatric intern and resident an opportunity to study the subject. The pediatrician loses, thereby, a valuable stimulus for active interest in mental hygiene and its problems. The committee feels that it should be its function and the function of the Academy as a whole to stimulate more adequate training and a more active interest. The committee further feels that the responsibility for these activities rests first with the chiefs of the pediatric departments of the medical schools and children's hospitals and, second, with pediatricians as a whole.

The committee therefore recommends:

I. Adequate training in medical schools as follows:
   1. Instruction during the first two years in medical school to include lectures on mental health.
   2. A formal course on mental growth and development, the mental aspects of various disease conditions, and common mental hygiene problems during the last two years of medicine. The chairman of the Educational Committee of the National Committee for Mental Hygiene suggests that such a course should be at least twelve hours in length.
   3. The use of a well-baby clinic as a means of teaching mental health to children.
   4. A mental health clinic in the pediatric department.
   5. Cooperation between the pediatric and psychiatric departments.

II. Adequate training of the pediatric intern and resident as follows:
   1. An opportunity to work in a mental hygiene clinic during a part of his internship or residency.
   2. An opportunity to attend seminars conducted by staff men qualified to give them the proper attitude towards mental health.
   3. An opportunity to study mental health and development in well-baby and older children's clinics.

III. In order to stimulate a more active interest in mental hygiene among pediatricians and to bring to their attention the valuable information found in medical literature, other than pediatric journals, it is suggested that a program be worked out for publication, extending over a period of several years, dealing with pertinent facts on mental health. These articles are to be published in THE JOURNAL OF PEDIATRICS. The Committee is now working on that program.

The committee welcomes suggestions from all members of the Academy and feels that the support and cooperation of all members is essential to the successful carrying out of the above program.

Respectfully submitted,

BERT I. BEVERLY, Chairman

C. A. ALDRICH
FREDERICK H. ALLEN
HORTON CASPARIS
BRONSON CROTHERS
GEORGE MOHR
ARTHUR H. PARMELEE
VICTOR E. STORK

Report of the Committee on Nursing Education in Pediatrics

While there has been no meeting of the entire committee, the chairman and secretary of this committee have been in conference. There has been consultation with Miss Corinne Bancroft, who is a member of the committee on the child in nursing education of the National League of Nursing Education. At this meeting there was discussed the question of the minimum requirements of instruction necessary in graduate training of nurses in pediatrics. No final decision was reached, and it was felt that the committee needed additional information. It was decided to request Miss Bancroft to secure a complete report of the opinion of the committee on nursing education of the National League of Nursing Education and subsequent meetings would then be held to discuss this material.

It was also thought that further study should be made of the requirements in undergraduate courses for nurses in pediatrics. Material will be gathered for this study and a report made later.

Signed,

A. GRAEME MITCHELL, Chairman

Report of the Committee on Revision of the Pharmacopoeia

This committee has presented a prospectus for a book on pediatric therapeutics and likewise has recommended that the Academy ask for formal application for membership in the United States Pharmacopoeia and National Formulary Convention, to be held in 1940.

Respectfully submitted,

ISAAC A. ABT, Chairman
WILLIAM N. BRADLEY
BERNARD FANTUS
H. H. PERLMAN
LOUIS W. SAUER

Report of the Committee on School Health and School Health Education

During the past year two new organizations concerned with school health programs have been formed by a reorganization of three groups. In June, by a merger of the American Physical Education Association and the Section on Health and Physical Education of the National Education Association, the American Association for Health and Physical Education was organized. This association is a department of the National Education Association. In October the American Association of School Physicians adopted a new constitution and by-laws and became the American School Health Association.

The American Association for Health and Physical Education has a very large membership of physical educators and a smaller active group of health educators, and it aims to develop active sections in other special fields such as medical and nursing services. It would seem that this association has an important function to perform particularly with reference to informing teachers, principals, and school administrators as to the progress of school health program development and in coordinating the various physical education activities with the health education and medical and nursing service activities in the schools.

The American School Health Association is a smaller organization including most of the state and city directors of school health and many school physicians. Its new constitution admits dentists, nurses, public health workers, nutritionists, mental hygienists, and health educators on the same basis as physicians, but requires adequate training in the basic medical sciences for membership. Conducting its annual meeting and activities as it does in close collaboration with the American Public

Health Association, it has a particular responsibility for the development and maintenance of professional standards for personnel and service through the coordination of the many special groups concerned with the various aspects of school health programs for which they were especially trained.

There is such a variety of other organizations who are concerned with some special aspect of the health of the school child that it is apparent that some organization is needed to coordinate the special services of various contributors to school health program development. Such organizations as the National Society for the Prevention of Blindness, the American Association for the Hard of Hearing, the National Organization for Public Health Nursing, the National Tuberculosis Association, the National Committee for Mental Hygiene, the American Heart Association, the American Dental Association, the American Society for the Promotion of Dentistry for Children, and other national groups continually give stimulus in developing standards and promoting interest in these special services. The American School Health Association through its relations with the American Public Health Association provides the facilities for coordination of these special contributions for the use of state, city, county and other public health officials.

The committee of the American Academy of Pediatrics feels that at the present time its function should be the interpretation of the viewpoint of the pediatric profession to these various groups and bring to pediatricians some of the trends and activities of school health associations and the contributing special organizations.

In our last report we pointed out the tendency of school and other professional leaders to expect that the school examination can meet the whole need for health examination. To correct this tendency there is need for our best pediatric leadership, and physicians who appreciate the importance of continued medical supervision of children must counteract such unsound trends. Your committee has had representatives attend meetings of the various national groups who influence school health program policies and have discussed this problem. The section, "Principles," in the last report of your committee was presented to the Committee on School Health of the Child Hygiene Section of the American Public Health Association and given such approval that it was incorporated in the report of the committee and published in the year book of the American Public Health Association with credit to your committee. We believe that many individual members of the Academy can influence school health program policy through the facilities of organized medicine in their community, through membership on boards of education and health, and through the organization of medical advisory councils for school programs. The following discussion is presented as a further indication of trends which our members can influence through community activity.

The emphasis upon periodic health examinations by the medical profession has, no doubt, had its influence in developing this excessive reliance upon the school medical service. A false sense of security from school examinations has resulted from a lack of sufficient medical guidance of the program. Too often physicians have been employed by school and health authorities merely to make examinations rather than to interpret the child's need and to act as medical advisors to the school authorities. The nonmedical professional leaders have accepted the health examination as important, but they have not recognized their own inability to judge the limitations of the service nor the possibilities of more adequate health supervision. They have not understood that the health examination "is not an isolated event purchasable wholesale in mechanized ways, it is important but only incidental to a well-rounded service of preventive medical care through life."

We may expect that school authorities will not develop an educational program that will protect the public against excessive reliance upon school examinations until we have given proper emphasis to the reasons for examinations by private

physicians. The people who can afford health supervision by their own pediatrician certainly should have more education along this line through the schools. The New Jersey Fellows have prepared for distribution to parents a leaflet, "A Study of the Minimum Desirable Standards for the Health Supervision and Care of Infants and Children," in which the frequency of health supervision visits for various age groups is considered. The average medical practitioner must recognize too the need for more thorough attention to health advice and educational procedure for those who do come to him for a health examination.

Another trend in schools that should be appreciated by the medical profession is the greater number of schools which give more time to the routine examination and who invite parents to attend the examination. As the rapid march-by inspections are replaced by more careful examinations in schools, the need becomes greater for education of the public regarding continued health supervision. The better the school service the more difficult it is for the school authorities and the public to interpret properly the limitations of the service and the advantage of personal or private preventive medicine. This tendency, no doubt, has led to some unwarranted fear on the part of a few practitioners that the schools would take over personal preventive health service and leave no opportunity for the development of this service by the private practitioner.

It must be recognized that it is natural for school authorities to want the public to appreciate the service provided through the school budget or through the cooperation of the education department, and so they themselves are likely to believe the service in their school is more adequate and complete than it is. It is not surprising that they should have a tendency to interpret the school medical service as offering more than is possible without any intent to exaggerate the value of the school service.

A proper evaluation of both school and private services is also made more difficult when no attempt is made to define the limitations of each particular school service to the educational authorities and to the public. Physicians have accepted the responsibility of examining large numbers of children in school without clearly differentiating the difference between such mass examinations and a private office service. We should recognize that private office health examinations have too often not met our best standards. So it is apparent that organized medicine must through advisory committees and through assistance on school problems gain sufficient influence that the limitations of the school service may be understood by the school authorities. The schools must in turn interpret the service properly to the public.

School authorities generally recognize the importance of education for proper attitudes and so may be led to understand the importance of educating both children and parents to want the kind of individualized service that is possible when the physician continues supervision over a period of time. No doubt the educator will thus appreciate the importance of the highest standards of continued service when he has had the service explained in connection with the care of his own children.

Of course, the problem will not be solved by limitations put upon the school service. More thorough study of each child by the school physician is essential for improving the advice given to teachers and parents in an educational program. In fact, an educational program by the school physician should provide no competition with a private office service. The physician who meets the parent in school can guide in the use of community medical resources, he can advise parents who might try unwisely to save on doctor's bills; he can increase the demand for preventive medicine; and he can point out the need for care of trivial ailments and the risk of ignoring the early signs of ill health. If the fundamental purpose of the service of the nurse and physician in the schools is to be education, we shall not restrict this educational program.

We should make clear that the physician can be more than an examiner in the schools. A school medical advisor can bring the contributions of the private practitioner to apply to the individual needs of his patient for guidance in the classroom. He can guide the teachers in training school children for improved attitudes about medical service. A medical advisor is needed to interpret the health education needs of pupils and parents to the teachers. The unreasonable fear of surgery, the superstitious belief in drugstore medication, the seeking for panaceas, the use of the physician as a last resort, and the failure to return to the physician when clinical study and diagnosis are needed are some of the common attitudes which every physician recognizes as neglected aspects of education. We should make clear to the school authorities and the public that more time could be used by the physician in the school without extending his service to those health examinations that could be more effective as a part of continued supervision by private physicians.

The summer round-up program of the National Congress of Parents and Teachers is an example of the critical situation needing organized pediatric guidance to determine future policies. Every physician is familiar with the round-up of children into a clinic by Parent-Teachers' Association members and the rapid file of children before a charitably minded physician who wished to help the mothers by looking for physical defects before school opens. One physician after another has become disgusted with the excessive demands for looking over large groups of children, but other physicians have taken their places. The Round-up was regarded as a demonstration, but after years of demonstration an advisory committee made up of experienced public health workers has advised the National Congress that the emphasis should be first upon immunization and then upon consultation with the private physician rather than an isolated wholesale procedure for finding deviations from a supposed normal child.

In many places this service has now been taken over by the school or as a part of the school medical service. It is not easy to turn the service back to the private physicians even if they are willing to give examinations in their private offices at reduced rates or free to the indigent.

The leadership in the National Congress of Parents and Teachers is urging local Parent-Teachers' Associations to seek and follow the advice of organized medicine. Parents need education as to the value of continued health supervision. Many local Parent-Teachers' Associations want guidance in modifying their summer round-up program. We should provide further leadership to use interest for sound public education.

Respectfully submitted,

HAROLD H. MITCHELL, Chairman
ROCKWELL M. KEMPTON ARTHUR E. WADE
M. HINES ROBERTS ESTELLA F. WARNER
A. CLEMENT SILVERMAN LEROY A. WILKES
CLIFFORD D. SWEET

Report of the Council for Pediatric Research

The council opened its office a little over a year ago. Its first aims were to acquire information regarding research facilities and activities in clinics and laboratories throughout the country and to get in touch with possible donors of research funds, and acquaint them with the reason for the council's formation, its organization, and its proposed activities.

Information regarding laboratories and clinics has been gathered partly by personal visits of the secretary and partly by means of a questionnaire sent to quite a

large list of institutions. By these means a fairly complete index has been built up of laboratories and clinics engaging in research bearing on pediatrics, their personnel and equipment, resources, special research interests, and investigations now in progress. This index will be amplified by other personal visits as opportunity arises. The secretary is aware that any such method of collecting data will miss some more or less independent investigators and would be glad to hear from any who have not been reached.

Contact with possible donors has been sought, both by letter and by personal visit to organizations known or supposed to be interested in subsidizing investigation. A complete list of such organizations is hardly possible, but various means have been used to reach at least the most likely prospects. Many contacts have been made; a number of commercial firms have sent representatives to the council's office to inquire into its purposes and methods, while others have expressed by letter sympathy with our ideas. Almost without exception the expressions of such organizations have been favorable.

These contacts with representatives of manufacturing firms have given the council a good deal of information regarding the problems with which it is attempting to deal. An obvious fact is that uncertainty regarding business conditions is very definitely limiting expenditures on research projects. This was to be expected. An apparent fear on the part of some less informed houses that the council may turn out to be "just another racket" is perhaps not surprising, but will probably be allayed in time. Two conditions of which we were aware will limit the possible scope of our activities. One of these is the fact that several of the larger houses have supervisors of research, quite capable of placing their research grants under most circumstances and having little need of the council's help. Another is the practice of making good-will grants on solicitation by clinics and laboratories. This is a nuisance to the manufacturers, but hard to check. The council may hope to have some effect on it in time and to divert some of this money to better purposes. There is also some evidence of what might be designated tacit opposition to the council on the part of investigators who seem to feel that they will have a better chance of obtaining large grants if they can deal directly with the grantors rather than through the mediation of the council. The council has no wish to interfere with established relationships between investigators and donors and sees no reason for this feeling.

Actually, we are just beginning to have definite projects brought to us which will probably result in research grants of some importance. Several of these are now in hand which we expect to handle successfully. Our experience has shown that, if we are to make a satisfactory showing during the two years of the grant from the Carnegie Corporation, we shall need assistance from Fellows of the Academy and others interested in what we are trying to do, in referring possible donors to us until we are better known. It is in this way that our best contacts have been made. It would seem that some commercial organizations need assurance of the disinterestedness and good faith of the council from their personal acquaintances in the profession.

In addition to its activities regarding the allocation of funds for research, the council is seeing some indications of other possible service within its scope. A number of the foundations have shown interest in our project from the start, and some of them have shown a desire to make use of the information we have been gathering which no one else seems to have. We have been approached also as to the possibility of our taking an active part in the direction of one quite ambitious long-term study, which if carried through, should be of considerable importance.

We have not yet had opportunity to make use of our information for the purpose, which seems very desirable, of coordinating research in certain fields, and helping to eliminate waste motion and duplication, which we have reason to know exists to a considerable extent.

Altogether, while we have not had such prompt success as we might have hoped, we feel that our idea is sound and that we shall have an increasing demand for our services. In the meantime, we may be said to be acquiring a technique in a rather difficult field.

Respectfully submitted,

THOMAS B. COOLEY, Executive Secretary

No reports have been made by the following committees:

Committee on Cooperation With Medical Groups and Societies

Committee on Legislation

(No matters have been referred to the above two committees during the past year.)

Committee on Neonatal Morbidity and Mortality

(Owing to the death of the chairman and reorganization of this committee, there is no report.)

SEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

NEW YORK, N. Y., JUNE 3-5, 1937

Round Table Discussion on Anemia of the Newborn

Dr. Hugh Josephs, Baltimore, Md., Chairman
Dr. Thomas B. Cooley, Detroit, Mich.
Dr. Louis K. Diamond, Boston, Mass.

CHAIRMAN JOSEPHS.—Our present conception of anemia of the newborn is a merging of several lines of observation. First, there is the pathologic term "erythroblastosis fetalis" first applied to cases of hydrops and for long confined to pathologic literature, scarcely more than an obstetric curiosity. Second, there was "icterus gravis" long used for certain severe and usually fatal cases of jaundice and recognized as frequently occurring in successive pregnancies. Tissue erythroblastosis was described in cases of icterus gravis about 1916. Following this there developed a gradual realization that icterus gravis with erythroblastosis was closely related to hydrops of the newborn with erythroblastosis. Third, "anemia of the newborn" developed quite independently following Ecklen's description of a case in 1919, though ten years earlier Buchan and Comrie had described the condition. Both these reports describe easily recognizable cases of what is now called "erythroblastosis fetalis," the condition that will form the principal topic of discussion today. Many of the cases reported as anemia of the newborn belong to this group, but the relationship to icterus gravis and erythroblastosis was unrecognized until 1931.

The first source of confusion then is in nomenclature: "erythroblastosis," a term used to describe a pathologic picture also used to designate a disease entity;

"icterus gravis," a descriptive term used also as the name of a disease; "anemia of the newborn," another descriptive term, the vaguest of all, employed as if all the cases to which it could be applied belonged together.

These three terms are often used as if they meant the same thing; herein lies a second source of confusion, for they are not absolutely synonymous. As has been pointed out, icterus gravis, a purely descriptive term, is used as if it designated a disease. Erythroblastosis is, however, only one of the conditions associated with icterus gravis although probably the most common, especially in familial cases. Severe icterus may result from sepsis and severe liver damage of unknown cause, which may sometimes be familial. Anemia and some degree of erythroblastosis may occur in these cases, and it is sometimes difficult to decide where to classify a case.

Similarly there are many cases of anemia of the newborn which clearly do not belong to the erythroblastosis group, and there are others without erythroblastosis but with increased hemolysis; thus one may be in doubt as to how to consider them.

A third source of error arises from the fact that the distinction between normal and pathologic is not as sharply defined as we should like to have it. There is scarcely a thing that is considered characteristic of anemia of the newborn with icterus gravis and erythroblastosis that does not occur normally. The difference is rather quantitative than qualitative. Erythroblastosis is often present at birth normally and occasionally the numbers may increase to what is usually considered pathologic. The difficulty of distinguishing icterus gravis from physiologic icterus is, of course, well known; the speed with which the red cell count and the hemoglobin content fall after birth may vary within wide limits, and not a few cases of so-called anemia of the newborn may be considered an exaggeration of the normal with quite as much reason as something essentially pathologic.

Out of all this confusion there has been separated a group of cases in which the symptom pattern is repeated over and over again and which has received the name "erythroblastosis fetalis." We call this condition an entity and talk of it as a disease because the clinical course and the histologic picture are similar, but we have no reason to assume that the process giving rise to the clinical and pathologic picture is the same in all cases. It is of course well known that syphilis and sepsis may reproduce the picture of erythroblastosis fetalis in all details. What we call erythroblastosis fetalis is what remains after the cases with syphilis and sepsis have been excluded. The exclusion of cases for which some explanation has been found is no more than a convenience leading to the grouping of cases that still await explanation but unfortunately has led to the labeling of the unexplained cases as "primary." The tendency to consider a pathologic end result as a disease is an important source of confusion. This point will be considered more fully in the discussion of etiology.

In the discussion that follows, it will be convenient to treat "erythroblastosis fetalis" as a disease entity. It must be remembered, however, that we know little of the essential nature of the condition, i.e., of the processes which give rise to the pathologic changes or the etiological factors that influence these processes.

DR. DIAMOND.—The following discussion of the clinical aspects of anemia of the newborn is based upon personal experience with 80 cases of erythroblastosis fetalis, 35 cases of sepsis in the neonatal period of life, resulting in anemia, 4 cases of anemia without jaundice or erythroblastosis (that is, of the aplastic type) and a large but uncounted number of cases of anemia developing later in the newborn period.

To dispose first of the better known types of anemia in the newborn, that is, the last three mentioned above:

1. Anemia developing later in the newborn period, by which we mean after the third month of life, is fairly common and has been relatively well studied. The

chief causative factors are, first and foremost, infection; second, prematurity and multiple births; third, dietary deficiency in either the mother or her offspring; and fourth, congenital malformations of the gastrointestinal tract and other systems of the body. We may forego discussion of anemia due to these factors since they are relatively well understood.

2. Anemia without jaundice or erythroblastosis, and incidentally without splenomegaly or hepatomegaly, that is, an aplastic type of anemia, is the least common of the blood disturbances of this age group. Of the four cases seen by us, three were in infants who had an aplastic bone marrow, proved by biopsy, and who required regular transfusions for the preservation of a blood level consistent with life. They first showed evidence of deficiency in hematopoiesis in the third to fourth month after birth. None of them was anemic at, or immediately after, birth. These three infants have been kept alive now for a period varying between one and five years, by means of transfusions given every two months and have shown no tendency to improve. The fourth infant in this group had a malignant hemangioendothelioma invading the bone marrow and causing an aplastic anemia.

3. Anemia due to sepsis and infection is also fairly common in the newborn infant. This factor therefore should always be excluded before the diagnosis of erythroblastosis or of aplastic anemia is accepted. Congenital syphilis is very likely to resemble the symptom complex which has been designated erythroblastosis fetalis. We have seen eight infants who at birth showed jaundice which increased in severity later, marked splenomegaly and hepatomegaly, increasing anemia through the neonatal period, and tremendous numbers of immature erythrocytes and leucocytes. Roentgenograms, blood serology tests, and in a few instances post-mortem examination of the tissues, established the diagnosis of congenital syphilis as the cause of these abnormal findings. Since specific treatment, as well as transfusion, was indicated in such cases, it was highly important that this specific disease be considered when the symptoms grouped above appeared in the newborn infant. Of the less well-known infectious agents colon bacillus not infrequently causes severe anemia, enlargement of the liver and spleen, and anemia in the newborn. We have seen two instances of acute pyelonephritis with colon bacillus bacteremia and jaundice and anemia, ending fatally in the first week of life. On the other hand, nine such patients have recovered following the usual supportive measures, including transfusion. Streptococcus or staphylococcus omphalitis, peritonitis, and pneumonia have accounted for the remainder of the cases in this group, except two cases of malaria occurring in the second month of life in infants who had hemorrhagic disease of the newborn and had been transfused with blood from parents suffering from latent chronic malaria.

To turn finally to the symptom complex known as erythroblastosis fetalis: This gained increasing attention recently because it is a relatively new disease in point of view of general medical interest. Also, increasing numbers of cases are being recognized which have been previously overlooked or erroneously diagnosed. Finally, with improvement in diagnostic ability there has been a satisfactory decrease in the mortality, as earlier and more vigorous therapy has been adopted.

We have listed for discussion under this heading, universal edema of the fetus, familial icterus gravis, erythroblastosis fetalis as described by Schridde (that is, from the pathologists' viewpoint), and anemia of the newborn. The question arises immediately, Are these manifestations of a single disease process, and if so, why is there so much disagreement concerning this point? I firmly believe that if every physician who sees such cases could play the role of the family doctor and see the mother of the child during her period of gestation, know her history well, attend the delivery, and make observations in regard to the infant immediately after birth, as

well as the placenta accompanying it, and then follow the blood changes as well as the changes in the tissues of the fatal cases, there would not be any question as to the identity of these symptom complexes. The difficulty has been that each specialist, that is, the obstetrician, the pathologist, and the pediatrician, has described that portion of the disease which has happened to come to his particular attention. The obstetrician has described the cases of universal edema of the fetus and familial icterus gravis with death in the first few days of life; the pathologist, the tissues of the stillborn infant with edema or of the infant with familial icterus gravis. The pediatrician, who usually does not see these two types of cases in the early stages and who rarely has the opportunity to examine the tissues in such cases, describes the later stages of the condition, when the anemia may be the most important symptom and the jaundice be either stationary or fading.

In our 80 cases we have been fortunate in having the cooperation of the obstetrical department under the supervision of Dr. Irving at the Boston Lying-in Hospital, of the pathology department under Dr. Wolbach, Dr. Farber, and Dr. Hertig, and of the pediatrics department under Dr. Blackfan and under Dr. Clifford at the Lying-in Hospital. Our observations, therefore, are a composite, not only of the opinions of all these individuals, but of the material available from before birth, through delivery, and into the neonatal life of the infant.

The typical picture of erythroblastosis fetalis in the moderately severe form may be as follows: In about one case out of three the mother may give a story of previous pregnancies ending in the birth of stillborn infants or infants dying with jaundice shortly after birth. In such cases an interesting corollary is the mother's story that fetal movements become lethargic and may even cease entirely in the last few days before delivery. At birth jaundice in the skin of the infant and occasionally a yellow orange hue to the vernix caseosa covering the infant may be noted. Also occasionally the placenta is enlarged one and one-half to two times the normal size. There may be a slight to moderate amount of edema demonstrable in the child's subcutaneous tissues. The liver and the spleen are both moderately enlarged. Occasionally petechiae appear spontaneously, and ecchymoses and free bleeding in the first few days may suggest hemorrhagic disease. The cord blood or blood from the capillary bed may show 50 to 100,000 or more nucleated erythrocytes. Anemia, though sometimes present at birth, more usually first appears in the first twenty-four hours after birth and becomes progressively more severe thereafter. In general, the slower this anemia in its appearance and development, the better the outlook, since such cases are relatively milder, with less jaundice, no edema, no petechiae, and fewer erythroblasts in the peripheral blood.

The milder types of this disturbance frequently escape notice during the first few days after birth and sometimes even during the first few weeks. Since icterus in such cases is either so mild and transitory that it passes for the ordinary icterus neonatorum and since blood examination for nucleated erythrocytes is not necessitated by the appearance of any other symptoms of the condition, the first sign of the disturbance may be the residual anemia which is present in all infants with the disturbance and which shows itself by a progressive pallor of the skin and mucous membranes. If a blood examination is not performed until the second or third week of life, there may be very few immature erythrocytes and merely an aplastic type of anemia.

A discussion as to pathogenesis and etiology is purposely avoided here. It is hoped, however, that the objective signs and symptoms which have been observed not only in these 80 cases but in the large number described in the literature will be explained by the later discussion. As a basis for this, certain other findings made in our personal contact with this disease will now be enlarged upon, and the obvious questions arising from this will be answered as far as possible.

As regards the inheritance of this condition, very little can be said until further studies like the recent one by Macklin have been made. I should like to call attention to the paper now in press by Hellman and Hertig on the subject of erythroblastosis as seen at the Boston Lying-In Hospital. Here an excellent discussion of the hereditary factor is given. In our own cases 35 per cent showed a positive family history. In general it may be said that a woman may have a child with erythroblastosis and yet have subsequent pregnancies result in normal children. However, after the birth of an infant with universal edema, the chances are better than 50 per cent for the recurrence of this abnormality. After the birth of two or more children with erythroblastosis and severe jaundice, the chances are better than 70 per cent for the recurrence. In such cases sterilization may be considered advisable.

The disappearance of erythroblasts from the peripheral blood is often very rapid. We have seen the number drop from 100,000 per cubic millimeter to 20,000 at the end of twenty-four hours and less than 1,000 at the end of forty-eight hours. With transfusion this disappearance may be even more rapid, so that following one transfusion no erythroblasts may be found.

The degree of icterus which develops in any given case is probably the result of several factors: the functional capacity of the liver to excrete bilirubin, the rapidity of destruction of abnormal cells, as well as the number of these cells. Therefore in an infant with a relatively mild degree of the condition in which the numbers of abnormal cells are not too great, their destruction not too rapid, and the functional capacity of the liver, which is notoriously poor at the time of birth, not too inefficient, no great degree of jaundice, that is, not much more than the normal child usually shows, need appear. However, on the basis of relatively few examinations in these milder cases it is our feeling that every case of erythroblastosis has an increase above normal in the bilirubin content of the blood. The hemorrhagic tendency has been found only in the severely affected patients, as those with universal edema and early and severe icterus gravis. In these cases it is associated not only with the prolongation of the bleeding and clotting times but also with lowered platelet count and pathologically with thrombi of nucleated red cells in the final capillaries. Anemia has been found in every case seen by us. It may vary from a level just below 3,000,000 per cubic millimeter to one less than 1,000,000. Although the anemia may not show itself in the first twenty-four hours, we should deny the possibility of a state of typical erythroblastosis existing with no anemia at any time. Some other cause for the erythroblastosis must be sought in such instances.

The cause of early death in the severe cases cannot be definitely stated at present. At post-mortem examination any one or a combination of the following may be blamed for it: free bleeding into the central nervous system and into the various cavities of the body; petechial hemorrhage in the brain due to thrombi of nucleated erythrocytes; extreme jaundice with toxemia, staining of the nuclei in the brain, and terminal convulsions; dilatation of the chambers of the heart and evidence of congestive heart failure; and anoxemia due to rapid development of severe anemia. Undoubtedly combinations of these are responsible for the early fatal cases rather than any one cause alone. As to the cause of death in the late cases, that is in patients dying after the first week of life, anoxemia due to profound anemia untreated by transfusion is the chief cause. Convulsions due to kernicterus may occur during the second and third weeks and may lead to death. Also intercurrent infection such as that produced by the colon bacillus in debilitated newborn infants or by any other pathogenic organism may occur at this time.

Spontaneous recovery probably occurs much more frequently than we realize, particularly in the group of infants who show no edema and very little jaundice in the first few days of life and who therefore are not suspected of having the disturbance. Recently by following the blood changes in offspring from families in

which other cases have occurred, we have seen examples of the milder forms of erythroblastosis with a tendency to spontaneous recovery or at least an early recovery with only a single transfusion.

Kernicterus was the unfortunate result in 5 of our 60 living children. Each of these had had very severe jaundice shortly after birth and although the profound anemia which developed responded to treatment by transfusion, this unfortunate residual complication existed after the child's blood had returned to normal. Spasticity and imbecility were the final results in all of them. My knowledge of the reason for the nuclear damage or staining, or both, is too incomplete to permit of any conclusions in regard to kernicterus.

As regards treatment, it is our feeling that transfusion with matched whole blood, given directly into a vein, is most satisfactory at present. Theoretically and on the basis of a few cases reported in the literature, blood serum or blood plasma, again best given intravenously, may be of some assistance. But since, as we have stated, anemia exists in every case, the erythrocytes can do little harm and may be of great value when put into the circulation of the child with erythroblastosis. Transfusion should be repeated as frequently as necessary to control the anoxemia due to profound anemia and also for its beneficial effect in controlling the hemolytic tendency evidenced by increasing icterus and lethargy. In the milder cases a single transfusion may be sufficient to tide the patient over the period of hemolysis as well as the period of functional aplasia which follows this. However, in the more severe cases as many as 15 or more transfusions have been given before recovery has occurred. A word of warning here: It is not necessary to keep the blood level up to 4 or 5 millions per cubic millimeter by repeated transfusions. A level of 2,500,000 to 3,000,000 has usually been found satisfactory to carry on all the functions of the body as evidenced by good appetite and gain in weight. Too frequent transfusion may not only increase the hemolytic tendency unnecessarily, but also may prolong the period of functional aplasia of the bone marrow. We have noted this in a few of our earlier cases. It is our feeling that the disease tends to run a self-limited course with spontaneous recovery at the end of this and that transfusion is necessary to tide the patient over the period of abnormal blood production and destruction.

We have insufficient evidence at present to settle the question as to whether kernicterus is a less frequent complication in the cases so treated but certainly it is not more frequent due to our method of repeated transfusions.

Although there seems to be some evidence for the fact that following transfusion there may be an increase in hemolysis when previously it had seemed to be subsiding, transfusions cannot safely be omitted in the face of anoxemia due to severe anemia. One therefore has to steer a medium course as to the frequency of transfusion and amount of infused blood so that on the one hand hemolysis is not accelerated and on the other, dangerous anemia does not occur.

The theory has been offered that erythroblastosis fetalis, which shows so strikingly a macrocytosis in the first few days of life, is an infantile form of pernicious anemia and should therefore respond to treatment with liver extract. Such a theory, however, is not borne out by our observations and our trial with liver extract in large amounts both orally and parenterally. Splenectomy may offer a means of reducing the hemolytic tendency. However, the operation is fraught with so many dangers in the newborn infant as to render it unfeasible in the very case in which it is needed the most, that is the one- or two-day-old infant with severe icterus, anemia, and cardiac enlargement. Blood or blood serum intramuscularly may have some beneficial effect, but the need for blood is usually so urgent that waiting for its absorption from the tissue spaces is often hazardous. Iron in the form of small amounts of iron sulfate has seemed to benefit some of our patients late in the course of spontaneous

recovery, when beginning cell regeneration appears. However, it is inadvisable to burden the infant's gastrointestinal tract with extra medication earlier in the course of the disease.

Finally, our conclusions as to the advisability of transfusion at properly spaced intervals in cases of erythroblastosis fetalis are based upon our accumulating statistical data. Excluding the infants with universal edema, all of whom have either been born dead or have died within the first few hours of life, our mortality rate during the first three years of our study was 33⅓ per cent, during the next three years 20 per cent, and during the last three years, 7 per cent.

DR. S. H. CLIFFORD (BROOKLINE, MASS.).—At the Boston Lying-in Hospital every baby born with yellow vernix is suspected of having erythroblastosis and is referred immediately to the Pediatric Service. In our experience only a small proportion of the babies with this so-called yellow vernix have actually been proved to have erythroblastosis. The most frequent cause of this staining has been found to be intrauterine asphyxia with the passing of meconium in utero which material stains the vernix and produces this color. I was of the opinion for a considerable period that by investigating the protective folds of the newborn, such as deep in the axilla, or in the folds of the groin, or in the region of the labia minora, or by retracting the prepuce on the boy babies, one could make the differential diagnosis between the yellow vernix of erythroblastosis and the staining due to some other factor. In other words, I felt that in erythroblastosis the yellow stain would penetrate to these areas, whereas, in meconium staining for instance, the vernix would still be white in the protected spots. I have since discovered that this assumption is not correct and I have recently seen a typical case of erythroblastosis with icterus gravus in which the vernix in the protected area was pure white while over the body it was golden yellow.

We are frequently confronted with the practical question as to whether a mother once having had an erythroblastic baby should necessarily avoid future pregnancy. When a given mother has had several babies with erythroblastosis, future pregnancies have been discouraged. When there have been other normal babies or when the baby with erythroblastosis occurs at the first pregnancy, the parents are advised that they have a greater chance of having an erythroblastic baby than a normal family, but, if they desire more children, they are encouraged to proceed. The reason for this is that, even though a second erythroblastic baby is born, the chances are all in favor of its not having a fatal hydrops type of the disease, and with immediate diagnosis and treatment, the prognosis should be favorable.

There remains a great deal to be done in the field of the congenital anemias. We are convinced that certain babies with congenital anemia are typical examples of erythroblastosis; yet there are other babies in whom this diagnosis is not tenable. We have seen several newborn babies with congenital anemia whose mothers have premature separation of the placenta or placenta previa, and we suspect that the separation of the placenta involved the fetal villi as well as the maternal and resulted in loss of fetal as well as maternal blood. This point has not as yet been proved.

CHAIRMAN JOSEPHS.—The incidence of the disease is of interest because of the discrepancy in numbers in the different cities, there being more cases reported in some sections than in others.

DR. DIAMOND.—I believe that the families become interested. The question of inheritance is not fixed.

CHAIRMAN JOSEPHS.—When the children recover, does the condition tend to recur?

DR. DIAMOND.—We have several patients who are now six to nine years old who are in good health. We have never known of a recurrence.

CHAIRMAN JOSEPHS.—What about the question of sterilization of the mother?

DR. DIAMOND.—We have two cases in which sterilization was recommended because in each succeeding child the condition was worse.

DR. H. M. GREENWALD (BROOKLYN, N. Y.).—I had an infant recently suffering from anemia of the newborn. Repeated transfusions and the administration of iron failed to bring about an increase either in the hemoglobin content or in the number of red blood cells. A hematocrit study showed the presence of a macrocytic anemia. Liver extract was given by injection and immediate improvement occurred. This was evident by an immediate and sharp rise in the hemoglobin content and in the number of red blood cells.

CHAIRMAN JOSEPHS.—How old was the infant when the treatment was started? What preparation did you use?

DR. GREENWALD.—Five to six weeks. A liver extract prepared by Lilly was used intravenously.

DR. DIAMOND.—We have used liver extract early in a few cases without success.

DR. C. H. SMITH (NEW YORK CITY).—We have had two cases in our hospital with no regeneration following transfusions and iron therapy. Liver extract was given orally and intravenously, and the children recovered.

DR. GREENWALD.—Hampson has used the injection of serum rather than whole blood in the treatment of icterus gravis neonatorum with excellent results. He believes that an antihemolytic substance which is probably absent in these cases is supplied when the parent's serum is injected and that this is responsible for the improvement. My own experience and the experience of others do not bear out the work of Hampson.

DR. COOLEY.—There may be a deficiency. When we use liver, we use the whole extract, and we feel that we get better results than with the P.A. extract.

DR. H. D. PASACHOFF (NEW YORK, N. Y.).—Dr. Diamond mentioned that erythroblastosis disappears early. In 1931 Dr. Leo Wilson and I reported a case of congenital anemia of the newborn, fatal on the fifth day, in which erythroblastosis was absent in the circulating blood. Post-mortem examination failed to show erythroblastosis. Two subsequent pregnancies in the same mother, both of which resulted in premature stillborn infants with universal edema, gave additional support to our diagnosis. There was no evidence of abnormal erythroblastic activity in these cases. We regard erythroblastemia as a secondary response to the anemia rather than as the underlying pathology in congenital anemia of the newborn.

DR. H. S. ALTMAN (NEW YORK, N. Y.).—Is there any advantage in giving transfusion to mothers of potential cases of erythroblastosis prior to the birth of the baby?

DR. PASACHOFF.—I would like to ask about your experience in prophylaxis in newborn infants by treating the mother. In one instance in which the mother was treated, her baby was normal; her three previous children had erythroblastosis. It may be a coincidence. I would like to ask Dr. Diamond how to explain an erythroblastemia at the time of recovery.

DR. DIAMOND.—Instances are on record in which whole liver extract has been given to these mothers, the birth of normal babies resulting. When the extract was stopped, subsequent pregnancies resulted in the birth of children with erythroblastosis; this is unconfirmed, however.

DR. COOLEY.—How great was the erythroblastosis at the time?

DR. PASACHOFF.—I had a case of a negro infant who showed a hemoglobin of 38 per cent on the eighth day of life, with one normoblast per 100 white cells counted. At twenty days the striking feature was the very marked evidence of regenerative activity present in the blood smear. There were 50 nucleated red cells per 100 white cells. We have had a number of such cases of congenital anemia of the newborn in which the erythroblasts in the circulating blood were few in number at the time of the most severe anemia, and with a considerable increase in their number at the time of recovery. The occurrence of this erythroblastemia late in the disease seems to corroborate the theory that erythroblastosis is a secondary feature rather than the basic disorder in this group of diseases.

DR. COOLEY.—I think the increase in erythroblasts may be due to a decrease in destruction.

DR. R. M. TYSON (PHILADELPHIA, PA.).—Are we to regard the extramedullary hematopoietic centers as cause or effect?

CHAIRMAN JOSEPHS.—This introduces a subject which is responsible for much argument, namely the mechanism of erythroblastosis. One group holds that the condition is essentially hemolytic and the erythroblastosis a response to the increased need. Opposed to this is the idea that the condition is essentially a disturbance in erythropoiesis and that hemolysis is a secondary phenomenon. Undoubtedly both hemolysis and erythropoietic disturbance are present more or less independently, and it is not unlikely that variations in their relative preponderance, as well as their varying duration, may go far toward explaining variations in the picture as well as apparent exceptions. I have no doubt that the erythroblastosis of the first few days is largely dependent on disturbance in erythropoiesis at least in the majority of cases. This disturbance, however, usually subsides relatively rapidly, and with it the majority of nucleated red cells in the blood. The hemolytic process is much slower to disappear, and it is not at all unlikely that the persistence of nucleated red cells may depend largely on the persistence of an increased need. At the time of beginning recovery there is often a moderate rise in the number of nucleated red cells accompanying a rise in reticulocytes—fairly clear evidence that now the erythroblasts are due to an increase in erythropoietic activity that heralds a return to normal. Why the rise in nucleated red cells at this time in Pasachoff's case should have been so much greater than usual I do not believe one can say. It seems likely enough that there may have been some residue of erythropoietic disturbance. This is, however, no more than a guess. The problem is too complex to admit of satisfactory discussion at the present time, but it is just such exceptions that Passachoff has brought forward that may lead to a better understanding.

DR. GREENWALD.—In answer to the question, "What is the earliest age at which a case of Cooley's anemia has been observed?" I may say this: It is quite likely that Cooley's anemia is not only a familial, but also a congenital disease; but the signs and symptoms of the disease cannot always be recognized until the child attains the age of five or six months. The following case may prove an exception. I have now on my service an infant who was born with a harelip and a cleft palate whose older brother and cousin died of Cooley's anemia. This infant was not icteric at any time. At two weeks of age a severe anemia and an enlargement of the liver and spleen were observed; the spleen and liver could be felt four fingerbreadths below the costal margin. The hemoglobin content at that time was 45 per cent and the red blood count was 2,000,000 with 21 per cent erythroblasts and 14 per cent reticulocytes. This anemia and the enlargement of the liver and spleen have persisted in spite of the usual treatment with liver, iron, and transfusions. The number of erythroblasts has decreased from time to time but they are never entirely absent. The reticulocyte count has been consistently high. Repeated roentgenologic

examination of the long bones and the skull have failed to show the changes characteristic of Cooley's anemia. Of course, the question arises, Is this an anemia of the newborn of the erythroblastotic type, or is this an early case of Cooley's anemia? This is a difficult question to answer at this time in view of the negative roentgenologic findings, but the familial history leads me to suspect that this may be an early case of Cooley's anemia.

DR. DIAMOND.—We have a family now with three children with Mediterranean anemia; the youngest, who was followed from birth, first showed blood changes typical of this condition at two months of age.

DR. COOLEY.—What causes kernicterus fetalis?

DR. DIAMOND.—Either primary damage to the brain nucleus followed by staining or vice versa. In patients who die with kernicterus there is increased liver damage. No definite information is available at present to explain the exact cause of kernicterus.

DR. J. M. LEWIS (NEW YORK, N. Y.).—Is kernicterus ever found in conditions other than icterus gravis?

DR. DIAMOND.—Cases of congenital obstruction of the bile duct have been studied at necropsy, and no evidence of kernicterus was found. Kernicterus may be found in Wilson's disease. One case of sepsis resulted in kernicterus.

CHAIRMAN JOSEPHS.—We could find in literature no report of cases of kernicterus occurring in conditions other than icterus gravis.

DR. COOLEY.—We have noted a report of kernicterus in a case of acute yellow atrophy of the liver.

DR. TYSON.—Are there instances on record of erythroblastosis in premature babies born dead? May this symptom complex begin and end during pregnancy so that at term the infant may show only an anemia?

DR. DIAMOND.—Only one case has been seen in a premature infant. The last question cannot be answered definitely. The condition is most common in full-term infants.

DR. J. A. RITTER (PHILADELPHIA, PA.).—Does the condition occur more frequently in general hospital wards rather than in private practice? Is there a deficiency factor? Have gastric content studies been made in these cases?

DR. DIAMOND.—As many cases occur in private practice as in general wards. Estimations of gastric acidity have been made in the recent cases but not enough reports are as yet available to be conclusive.

DR. JOSEPH STOKES, JR. (PHILADELPHIA, PA.).—What studies in chemistry of mother's blood have been done?

DR. DIAMOND.—There was no evidence of anything abnormal in work done on two cases.

DR. CLIFFORD.—Dr. Irving and Dr. Minot followed two cases very closely and could find nothing abnormal.

DR. RITTER.—Is there any relation between the macrocytic anemia of pregnancy and the causation of erythroblastosis?

DR. DIAMOND.—There has been no relation in cases that we have studied.

CHAIRMAN JOSEPHS.—In a review of the literature I have been unable to find any relation between macrocytic anemia in the mother and erythroblastosis in the infant.

DR. RITTER.—When the erythrocyte count in newborn infants becomes low, is there any change in the blood type?

DR. DIAMOND.—No change has been noted.

DR. TYSON.—Is there any relationship in hemorrhagic disease of the newborn and erythroblastosis?

DR. SMITH.—Is the so-called anemia of the newborn related to erythroblastosis?

DR. COOLEY.—Not all anemias of the newborn are due to erythroblastosis. Anemias due to acute infections, sepsis, and syphilis have been mentioned. Hemorrhagic disease of the newborn is a definite entity, though of unknown etiology. There seems to be a group of deficiency anemias in the newborn period, and in these cases it is often found that the mother has been gravely anemic during the pregnancy. I think that the type of hemolysis may be a valuable diagnostic criterion. In the anemias due to infection and in the deficiency anemias, the blood smears give the picture of marked increase in fragmentation. In true erythroblastosis there is no increase in fragmenting forms, though there may be striking anisocytosis. Fragility is likely to be somewhat increased, and there is a strong suggestion of the type of hemolysis met with in hemolytic icterus. We think that the abrupt cessation of the hemolytic process and the rapid improvement of the blood picture observed in three cases after splenectomy are good evidence that the spleen plays a role here much like that in hemolytic icterus.

Pathogenesis.—I should like to suggest a theory of the pathogenetic process involved. In the first place, there are evidently two types of cases, grouped according to when hemolysis begins. In one, hemolysis has been marked before birth, the vernix and the amniotic fluid are pigmented, and the child is born jaundiced. The cases with hydrops belong with this early group. In the other type the babies are born to all appearances normal, but within the first few hours after birth sudden, extreme hemolysis occurs, with rapid development of pronounced icterus. I think that we have primarily a state of polycythemia, due to a constitutional exaggeration of the fetal type of hemopoiesis, possibly with production of abnormal, unusually susceptible erythrocytes. In the first type, the spleen has reacted to this condition by a hyperactivity similar to that spoken of as "hypersplenism" in hemolytic icterus; in the second type this hyperactivity does not develop until the added stimulus of the birth changes supervenes. In either case, the result is a hemolytic anemia. If the child survives, the extramedullary foci disappear, splenic activity gradually returns to normal, and after a more or less prolonged period of marrow hypoplasia the whole picture gradually clears up.

Though we think that we have demonstrated that prompt splenectomy has the same prompt curative effect here as in hemolytic icterus, we are inclined not to advise it except in obviously grave cases. The operation offers serious surgical difficulties in so young a patient, and statistics of results of less drastic treatment are very satisfactory.

DR. DIAMOND.—In cases in which hemolysis began after the first few days there was no evidence of enlargement of the spleen. However, after transfusion splenic enlargement was noted and hemolysis became a prominent factor. Excessive hemopoiesis comes first and is followed by hemolysis.

DR. COOLEY.—There may be excessive hemolysis of transfused blood if hemolysis occurs by fragmentation. The important point in arriving at a diagnosis of anemia in the newborn is the determination of what is going on in the hemopoietic system.

DR. RITTER.—In transfusing patients with erythroblastosis is citrated blood used?

DR. DIAMOND.—We use citrated blood only and do not have any increase in untoward reactions. Usually 10 c.c. of blood per pound of body weight is given. In children showing marked anemia 20 c.c. per pound may be used.

DR. T. B. GIVAN (BROOKLYN, N. Y.).—What veins are used?

DR. DIAMOND.—This depends on the skill of the operator. In Children's and Infants' hospital we never cut down on a vein. In most instances scalp veins are used. Difficulty seldom arises if the technique is mastered. We use a 24 gauge needle with a Kauffman-Luer side arm syringe and a pressure 20 c.c. syringe. We never give blood into the superior longitudinal sinus; the ankle veins or the femoral veins may be used. Blood is not given by the drip method ordinarily. The transfusion is stopped if any evidence of heart embarrassment occurs; the remainder of the blood may be given in divided amounts.

DR. COOLEY.—We never give more than 15 c.c. of blood per pound of body weight. Veins on the dorsal aspect of the hands may be used. There is no reason why the internal saphenous vein could not be cut down on. Blood should never be given by the intraperitoneal route. In debilitated or morbid infants the blood may remain unchanged or unabsorbed in the peritoneal cavity following transfusion by this route.

DR. H. G. PONCHER (EVANSTON, ILL.).—In severely jaundiced cases, does transfusion cause any ill effect, from products resulting from destruction of blood?

DR. DIAMOND.—You would have to have parallel cases to answer definitely.

CHAIRMAN JOSEPHS.—There is probably no doubt that transfusion does add to the jaundice, but do not withhold it on this account because transfusion does have a definite value.

DR. L. S. FRIEDMAN (CINCINNATI, OHIO.).—Would you give a prophylactic transfusion to a normal appearing infant at birth?

DR. DIAMOND.—We have always waited for changes to appear before giving a transfusion.

DR. COOLEY.—I doubt the wisdom of transfusion before the appearance of anemia. If transfusion is given before anemia manifests itself, greater hemolysis may result, or a troublesome polycythemia may be produced. I have seen one death which may have been the result of premature transfusion.

DR. FRIEDMAN.—Is irradiation of the spleen useful in cases of erythroblastosis?

DR. DIAMOND.—Effects of irradiation are too slow in this condition to be of any value.

DR. COOLEY.—Since changes in the spleen are usually temporary, there is no need for splenectomy or irradiation in most cases.

DR. WALTER LEVY (NEW YORK, N. Y.).—Have there been any necropsy studies of the mothers of children with erythroblastosis?

DR. DIAMOND.—None reported or known.

DR. GIVAN.—Is erythroblastosis ever associated with congenital defects?

DR. DIAMOND.—Erythroblastemia may occur with other congenital defects such as obliteration of the bile ducts and congenital cardiac anomalies.

CHAIRMAN JOSEPHS.—I may mention Passachoff's case in which in addition to congenital atresia of the bile ducts there was also a typical picture of erythroblastosis.

Before bringing the discussion to a close, I wish to say a few words regarding etiology. I have arranged in a table the principal factors, known and hypothetical,

that should be considered in any discussion of anemia of the newborn. *Syphilis, sepsis* and *malaria* have already been thoroughly discussed. *Hemorrhage* as a cause of anemia is too obvious to need discussion, but I should like to emphasize one or two points. Purpuric manifestations and reductions of platelets are not at all uncommon in erythroblastosis. The case that Dr. Cooley cited earlier was particularly interesting because of the fact that thrombopenic purpura was present without any other of the manifestations of erythroblastosis fetalis, although from the family history we can be fairly sure that the condition was present. It has already been brought out that some of the cases of hemorrhagic disease of the newborn may have been cases of erythroblastosis with terminal hemorrhage.

Hemorrhage into the adrenals might be specially mentioned since it may go unrecognized, even when large enough to cause anemia. Recently I have seen a case with a cephalhematoma causing severe anemia. In these cases there may be jaundice and evidence of increased pigment excretion.

The rare possibility of leucemia and osteosclerosis need be no more than mentioned.

Congenital aplastic anemia has already been mentioned. A number of the reported cases of anemia of the newborn fall in this group, but, because of the relative slowness with which the anemia may develop, they may not be recognized until after the passage of several weeks. There is almost no literature on them. I can add two from my own experience to those which Dr. Diamond has mentioned. I should like to warn here against too indiscriminate diagnosis of aplastic anemia on the basis of absence of erythroblastosis and a low reticulocyte count. Cases with clear evidence of hemolysis may have no erythroblastosis, and normally there is a period in the second and third week of life in which the reticulocytes are at a very low point. The diagnosis of aplastic anemia should depend either on autopsy or on the continuance of the signs of aplasia beyond the third week. However, some degree of temporary hypoplasia may be a factor in cases without erythroblastosis, and even in some cases with erythroblastosis.

Congenital hemolytic jaundice has rarely been reported as a cause of anemia at birth; sickle-cell anemia never, to my knowledge. With regard to Mediterranean anemia I shall have to ask Dr. Cooley and Dr. Diamond what their experience has been.

So much for the etiological agents that are known to be capable of causing anemia at birth or shortly after birth. Since in the majority of cases with the clinical and hematologic picture of erythroblastosis these known etiological factors have been excluded, we are forced to turn to a consideration of more or less hypothetical possibilities. These are to be looked on not as cause of a disease, but as factors which may singly or in combination give rise to pathologic changes, the results of which are the syndromes that we call erythroblastosis or anemia of the newborn, or other names. There is evidence in favor of each of these possibilities as well as difficulties in the way of their acceptance, without making assumptions at present incapable of proof.

The first possibility is that of inherited defect affecting the baby. Of course, congenital hemolytic jaundice is just such a condition and is apparently capable of appearing at birth; it, or some other similar type of defect, may be present in some cases. In the majority, however, the complete recovery precludes this as a possibility. On the other hand, there are undoubted cases in which an inherited factor is clearly present, especially those in which the tendency to give birth to babies with erythroblastosis appears in several generations of the same family. What the nature of this inherited factor is and how and where it acts are entirely unknown. Moreover, only investigation of the future can determine how frequently it is to be considered a factor in these cases.

The second possibility is that of a failure in the development of the hemopoietic tissue, so that an earlier embryonic type of blood formation persists up to the time of delivery. This may be either constitutional or due to some factor associated with the pregnancy. It would be hard to understand a retardation that persisted for several months of intrauterine life followed by an acceleration sufficient to bring hemopoiesis to a normal level in three to four weeks of extrauterine life, unless the retardation has been caused by something closely associated with the pregnancy. Whether we are dealing with a failure to develop or a return to previous level due to something happening in the latter months of pregnancy, I do not believe can be decided at present. Because of the rarity of this condition in premature babies, as gathered from cases in the literature, I would personally incline to the latter view.

The third possibility, now almost universally abandoned, is that of some obscure infection. As a cause of erythroblastosis, anemia and jaundice in the newborn, of course, infection always remains a possibility; but, as a cause of the entity that we are discussing, infection is a very unlikely possibility. It would have to be something existing over a long period of time in the mother, without affecting her in any ascertainable way, and it would have to affect the baby at certain specific points. Actually syphilis is an infection capable of doing just this, and for this reason alone we cannot say that some other specific infection, at present unrecognized, is inconceivable.

The hypothesis that the condition is due to some intoxication associated with pregnancy, is at present the most widely held. It would explain some of the characteristics of the condition, such as its rapid disappearance after birth and its occurrence in successive pregnancies, as well as the pathologic picture. Also erythroblastosis has actually occurred in association with toxemia. Since in the majority of cases there is no evidence of toxemia in the mother to maintain this hypothesis we are forced to assume some hitherto undescribed intoxication which causes no damage except under conditions which exist on the fetal side of the placenta (e.g., anoxemia), or one arising from the placenta itself. This raises the question whether disease of the placenta itself may be a factor in these cases, a possibility that has not yet received sufficient attention in the literature.

Lastly we have the possibility that the condition is due to a deficiency. As in the case of intoxication we are compelled to make certain assumptions. In general, the baby develops at the expense of the mother, so that it is the mother and not the baby who gives evidence of deficiency. We may raise the question whether in these cases the placenta is impermeable, but, since these babies are not rachitic or scorbutic, the impermeability of the placenta must be selective. Or we may question whether the deficiency causes damage only under the condition existing in the fetus. It may thus be seen that to maintain the idea of deficiency leads to difficulties, but these difficulties are not very different from those encountered in maintaining the idea of an intoxication. On the other hand, the idea of a deficiency receives support from cases in which liver given to the mother during pregnancy has apparently prevented the occurrence of the condition in the baby.

This ends a rather sketchy discussion of etiology. Questions have been raised for which there is no answer today. Before we can begin to answer them we must know more than we do now concerning the placenta, not just the anatomic changes, but the physiology including such things as permeability and the part pathologic changes may play in the development of the fetus. We must also know more definitely the answers to questions raised today: the specific effect of transfusion, the relation of liver pathology to the picture, the effect of serum, the prophylactic effect of liver, and the influence of hereditary factors.

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